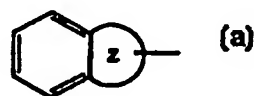
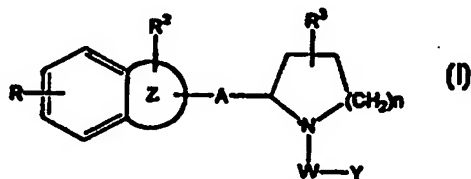




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 403/06, 401/06, 405/06, 409/06, 207/08, 207/10, A61K 31/40, 31/47		A1	(11) International Publication Number: WO 97/45424
			(43) International Publication Date: 4 December 1997 (04.12.97)
(21) International Application Number: PCT/KR97/00100		(74) Agents: CHOI, Kyu, Pal et al.; 824-20, Yeoksam-dong, Kangnam-ku, Seoul 135-080 (KR).	
(22) International Filing Date: 31 May 1997 (31.05.97)			
(30) Priority Data: 1996/19282 31 May 1996 (31.05.96) KR		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): C & C RESEARCH LABORATORIES [KR/KR]; 146-141, Amnyung-ri, Taean-ub, Hwasung-kun, Kyunggi-do 445-970 (KR).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): KOO, Bon, Am [KR/KR]; Dongsin Apartment #7-708, 627-1, Mok 3-dong, Yangchun-ku, Seoul 158-053 (KR). MIN, Jae, Ki [KR/KR]; Jangmi Manshun #101-203, 101-56, Maetan 1-dong, Paldal-ku, Suwon-shi, Kyunggi-do 442-371 (KR). HONG, Woo, Sang [KR/KR]; 979-21, Saeryu 2-dong, Kwonsun-ku, Suwon-shi, Kyunggi-do 441-112 (KR). RYU, Eun, Jung [KR/KR]; Dongbaekwoosung Apartment #1311-1501, Sanbon 2-dong, Kunpo-shi, Kyunggi-do 435-042 (KR). NAM, Woong, Hyun [KR/KR]; 410, Yuljeon-dong, Jangan-ku, Suwon-shi, Kyunggi-do 440-320 (KR). KIM, Jong, Min [KR/KR]; Ingaejuking Apartment #126-103, Ingaedong, Paldal-ku, Suwon-shi, Kyunggi-do 442-070 (KR).		Published With international search report.	

(54) Title: AROMATIC AMIDINE DERIVATIVES USEFUL AS SELECTIVE THROMBIN INHIBITORS



(57) Abstract

The present invention relates to a novel thrombin inhibitor which is effective even when orally administered. More specifically, the present invention relates to an aromatic amidine derivative represented by formula (I) and the salts thereof, which show potent selective inhibitory activity for thrombin in which (a), R, R¹, R², R³, A, W, Y and n are defined as described in the specification.

FOR THE PURPOSES OF INFORMATION ONLY

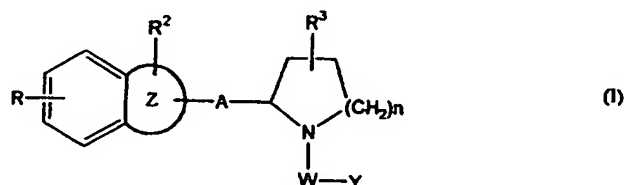
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

AROMATIC AMIDINE DERIVATIVES USEFUL AS SELECTIVE THROMBIN INHIBITORS

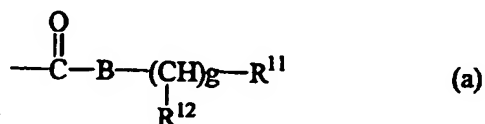
TECHNICAL FIELD

The present invention relates a novel thrombin inhibitor which is effective even when orally administered. More specifically, the present invention relates to an aromatic amidine derivative represented by formula (I) and the salts thereof, which show potent selective inhibitory activity for thrombin:



in which

R represents a group of formula or , wherein R¹ represents hydrogen, hydroxy, alkyl, alkoxy, alkylcarbonyl, alkylcarbonyloxy, aralkoxycarbonyl, or a radical of formula (a),



wherein

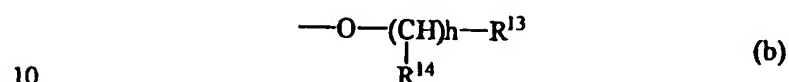
B represents oxygen or sulfur;

R¹¹ and R¹² independently of one another represent hydrogen, haloalkyl, alkylcarbonyloxy, dialkylamino, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring; and

g denotes an integer of 0 to 3;

R^2 represents hydrogen, hydroxy, halogen, carboxy, aminocarbonyl, alkyl, alkoxy, hydroxyalkyl, aminoalkyl, alkylcarbonyl, alkylsulfonyl, carboxyalkyl, aminocarbonylalkyl, alkoxyalkonylalkyl, or substituted or unsubstituted arylsulfonyl;

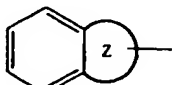
5 R^3 represents hydrogen, halogen, alkyl, hydroxyalkyl, carboxyalkyl, alkoxyalkonylalkyl, alkoxyalkonyl, carboxy, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, or a radical of formula (b),



wherein

R^{13} and R^{14} independently of one another represent hydrogen, alkyl, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring; and

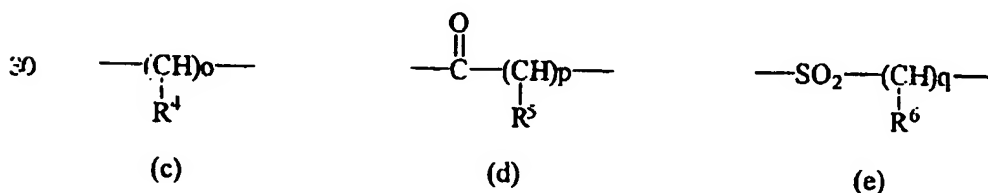
15 h denotes an integer of 0 to 3;

the group of formula  represents a radical selected from

20 the group consisting of indolyl, benzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, naphthyl, tetrahydronaphthyl, indanyl, dihydrobenzofuranyl and dihydrobenzothienyl;

A represents a saturated or unsaturated alkylene group having 2 to 4 carbon atoms, which may have 1 or 2 substituents selected from the group consisting of carboxy, alkyl, hydroxyalkyl, carboxyalkyl, alkylcarbonyl, alkoxyalkonyl and alkoxyalkonylalkyl;

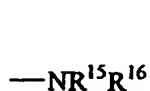
25 W represents a group of formula (c), (d) or (e),



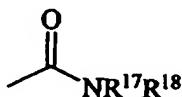
wherein

35 o , p and q independently of one another denote an integer of 0 to 3,

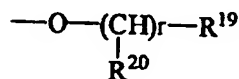
R^4 , R^5 and R^6 independently of one another represent hydrogen, hydroxy, carboxy, alkoxycarbonyl, substituted or unsubstituted arylsulfonyl, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring, or represents a group of formula (f), (g) or (h),



(f)



(g)



(h)

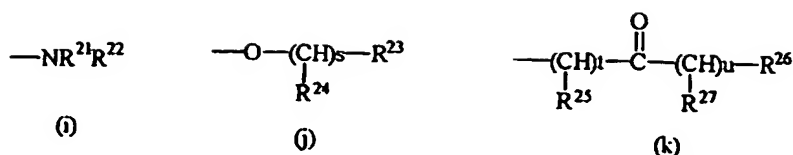
wherein

R^{15} , R^{16} , R^{17} and R^{18} independently of one another represent hydrogen, alkyl, alkylsulfonyl, carboxyalkyl, alkylcarbonyl, aminocarbonylalkyl, alkoxycarbonylalkyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring;

R^{19} and R^{20} independently of one another represent hydrogen, carboxy, aminocarbonyl or alkoxycarbonyl, or represents 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings; and

r denotes an integer of 0 to 3;

Y represents hydrogen or a 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings and which may be substituted on any atom of the ring with a substituent selected from the group consisting of oxygen, halogen, nitro, alkyl, haloalkyl, hydroxyalkyl, alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring, and a group of formula (i), (j) and (k),



wherein

R^{21} and R^{22} independently of one another represent hydrogen, alkyl, alkylsulfonyl, carboxyalkyl, alkylcarbonyl, alkoxycarbonylalkyl, or substituted or unsubstituted arylsulfonyl;

R^{23} and R^{24} independently of one another represent hydrogen, carboxy, aminocarbonyl, alkoxycarbonyl, or 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings;

R^{25} , R^{26} and R^{27} independently of one another represent hydrogen, hydroxy, thio, amino, carboxy, aminocarbonyl, alkoxy, alkoxycarbonyl, alkylamino, alkylsulfonylamino, alkenyl, alkoxycarbonylamino, cycloalkylamino, alkoxycarbonylalkylamino, substituted or unsubstituted arylsulfonylamino, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring;

s denotes an integer of 0 to 3;

t denotes an integer of 0 to 6; and

u denotes an integer of 0 to 8; and

n denotes an integer of 0 to 2,

provided that when each of g, h, o, p, q, r, s, t and u denotes number of 3 or more, the corresponding alkylene chain may be straight or branched.

The present invention also relates to a process for preparation of the compound of formula (I), and a thrombin inhibitor composition containing the compound of formula (I) as an active component.

BACKGROUND ART

Thrombosis is a pathological process in which platelets aggregation or a fibrin clot occludes a blood vessel. Anticoagulants interfere

with fibrin formation and are used for prophylaxis of thrombosis.

The blood coagulation system involves a number of zymogens (inactive enzymes) that are activated through a cascade of enzymatic reactions. The final step in coagulation is the formation of the fibrin clot from fibrinogen by a trypsin-like serine protease thrombin, which in turn is generated from prothrombin by the action of factor Xa. Accordingly, the blood coagulation enzyme thrombin plays a central role in hemostasis and thrombosis. Thrombin inhibitors are therefore expected to be effective anticoagulants by inhibition of platelets, fibrin formation and fibrin stabilization. It also activates factor V and factor VIII in a positive feed back reaction.

In recent years, numerous thrombin inhibitors have been developed as potential antithrombotic and anticoagulant agents, for example, tripeptide derivatives such as PPACK [D-Phe-Pro-Arg-CH₂Cl, Thromb. Res., 14, 969 (1979)], D-Phe-Pro-Arg, Boc-D-Phe-Pro-Arg, and D-MePhe-Pro-Arg [J. Med. Chem., 33, 1729 (1990)], DuP-714 [Ac-(D)-Phe-Pro-boroArg-OH, J. Biol. Chem., 265, 18289 (1990)], Efegatran [D-MePhe-Pro-Arg · H₂SO₄, Thromb. Haemost., 67, 325 (1992)], Inogatran [HOOC-CH₂-(R)Cha-Pic-Nag, where Cha : cyclohexylamine, Pic : pipelic acid and Nag : noragmatine, WO 93/11152, Blood Coag. Fibrinol., 7, 69 (1996)] and CVS-1123 [(CH₃CH₂CH₂)₂-CHCO-Asp(OCH₃)-Pro-Arg, WO 93/15756] and piperidine amide derivatives such as Argatroban [US 4258192, Thromb. Haemost., 18, 13 (1992)] and NAPAP [J. Biol. Chem., 266, 20085 (1991)]. But, they are not necessarily sufficient for practical use in view of oral bioavailability, inhibition selectivity for thrombin over other serine proteases, stability, duration of action and toxicity at the therapeutic dosages.

In view of the above, the present inventors have conducted intensive studies to develop potent thrombin inhibitors which are orally bioavailable, selective in inhibition of thrombin over other serine proteases and sufficient for practical use. As a result of such efforts, we have found that the compound of formula (I) exhibits excellent

thrombin inhibitory activity even when orally administered and has a high selectivity for thrombin in comparison to trypsin, and have thereby completed the present invention.

5

DISCLOSURE OF THE INVENTION

The present invention relates to an aromatic amidine derivative of formula (I), as defined above, and pharmaceutically acceptable salts thereof.

10

In addition, the present invention relates to a process for preparation of the compound of formula (I).

The present invention further relates to a thrombin inhibitor composition containing the compound of formula (I) or its pharmaceutically acceptable salts as an active component.

15

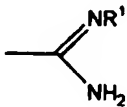
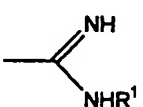
BEST MODE FOR CARRYING OUT THE INVENTION

20

The compound according to the present invention is represented by formula (I) as defined above.

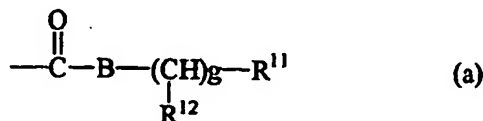
Preferred compound of formula (I) according to the present invention includes those, in which

25

R represents a group of formula  or , wherein

R¹ represents hydrogen, hydroxy, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₂-C₄ alkyl-carbonyl, C₂-C₄ alkylcarbonyloxy, or a radical of formula (a),

30



35

wherein

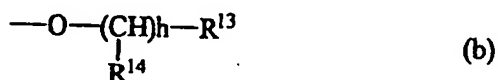
B represents oxygen or sulfur,

R^{11} and R^{12} independently of one another represents hydrogen, C_1 - C_4 haloalkyl, C_2 - C_4 alkylcarbonyloxy, C_2 - C_6 dialkylamino, or substituted or unsubstituted 6-membered carbocyclic ring, and

5 g denotes an integer of 0 to 3;

R^2 represents hydrogen, halogen, carboxy, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 hydroxyalkyl, C_1 - C_4 aminoalkyl, C_2 - C_4 alkylcarbonyl, C_1 - C_4 alkylsulfonyl, C_2 - C_4 carboxyalkyl, C_2 - C_4 aminocarbonylalkyl or C_3 - C_7 alkoxy-carbonylalkyl;

10 R^3 represents hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_4 hydroxyalkyl, C_2 - C_4 carboxyalkyl, C_3 - C_7 alkoxy-carbonylalkyl, or a radical of formula (b),



15

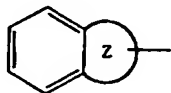
wherein

R^{13} and R^{14} independently of one another represent hydrogen or phenyl, and

h denotes an integer of 0 to 1;

20

the group of formula



represents a radical selected from

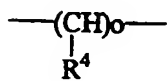
the group consisting of indolyl, benzofuranyl, benzothienyl, benzoimidazolyl and naphthyl;

25

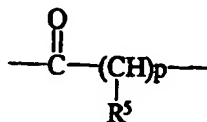
A represents saturated or unsaturated alkylene group having 2 to 4 carbon atoms, which may have 1 or 2 substituents selected from the group consisting of carboxy, C_1 - C_4 hydroxyalkyl and C_2 - C_4 alkoxy-carbonyl;

W represents a group of formula (c), (d) or (e),

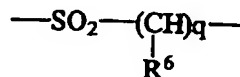
30



(c)



(d)

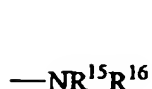


(e)

35

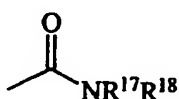
wherein

o, p and q independently of one another denote an integer of 0 to 3,
 R^4 , R^5 and R^6 independently of one another represent hydrogen, hydroxy,
 carboxy, C_2 - C_4 alkoxycarbonyl, phenylsulfonyl, or substituted or
 5 unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic
 or carbocyclic ring, or represents a group of formula (f), (g) or (h),

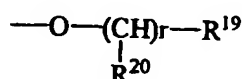


10

(f)



(g)



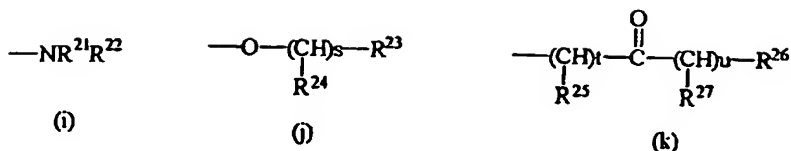
(h)

wherein

R^{15} , R^{16} , R^{17} and R^{18} independently of one another represent hydrogen,
 C_1 - C_4 alkyl, C_1 - C_4 alkylsulfonyl, C_2 - C_4 carboxyalkyl, C_2 - C_4 alkyl-
 15 carbonyl, C_2 - C_4 aminocarbonylalkyl, C_3 - C_7 alkoxycarbonylalkyl, or
 substituted or unsubstituted 3- to 5-membered saturated or unsaturated
 heterocyclic or carbocyclic ring,

R^{19} and R^{20} independently of one another represent hydrogen, carboxy,
 aminocarbonyl or C_2 - C_4 alkoxycarbonyl, or represents 5- to 6-
 20 membered saturated or unsaturated heterocyclic or carbocyclic ring
 which may be fused with other one or more 5- to 6-membered
 saturated or unsaturated heterocyclic or carbocyclic ring, and
 r denotes an integer of 0 to 3;

Y represents hydrogen, or represents 5- to 6-membered saturated or
 25 unsaturated heterocyclic or carbocyclic ring which may be fused with
 other one or more 5- to 6-membered saturated or unsaturated
 heterocyclic or carbocyclic ring and which can be substituted on any
 atom of the ring with substituent selected from the group consisting
 of oxygen, halogen, nitro, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4
 30 hydroxyalkyl, C_1 - C_4 alkylsulfonyl, phenylsulfonyl, substituted or
 unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic
 or carbocyclic ring, and a group of formula (i), (j) and (k),



wherein

R^{21} and R^{22} independently of one another represent hydrogen, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkylsulfonyl, $\text{C}_2\text{-C}_5$ carboxyalkyl, $\text{C}_2\text{-C}_5$ alkylcarbonyl, $\text{C}_3\text{-C}_7$ alkoxy carbonylalkyl or phenylsulfonyl,

R^{23} and R^{24} independently of one another represent hydrogen, carboxy, aminocarbonyl, $\text{C}_2\text{-C}_4$ alkoxy carbonyl, or 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with other one or more 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring,

R^{25} , R^{26} and R^{27} independently of one another represents hydrogen hydroxy, thio, amino, carboxy, aminocarbonyl, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_2\text{-C}_4$ alkoxy carbonyl, $\text{C}_1\text{-C}_4$ alkylamino, $\text{C}_1\text{-C}_4$ alkylsulfonylamino, $\text{C}_2\text{-C}_5$ alkenyl, $\text{C}_2\text{-C}_4$ alkoxy carbonylamino, $\text{C}_3\text{-C}_6$ alkoxy carbonylalkylamino, $\text{C}_3\text{-C}_6$ cycloalkylamino, phenylsulfonylamino, or substituted or unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring,

s denotes an integer of 0 to 3,

t denotes an integer of 0 to 6, and

u denotes an integer of 0 to 8, and

n denotes an integer of 0 to 2,

provided that when each of g, h, o, p, q, r, s, t and u denotes number of 3 or more, the corresponding alkylene chain may be straight or branched.

Typical examples of the compound of formula (I) which can be provided by the present invention are listed in the following Table 1.

Table 1.

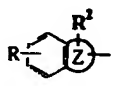
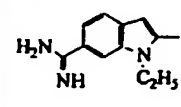

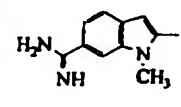
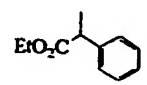
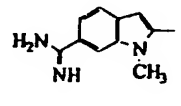
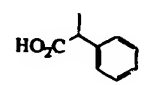
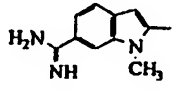

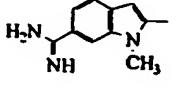

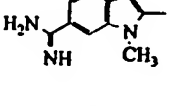

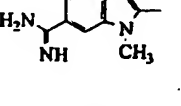
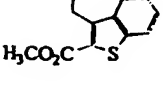
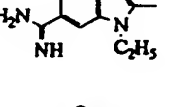
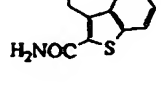
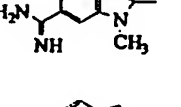
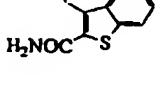
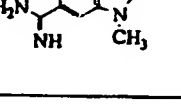
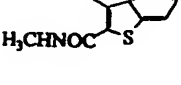
compound No.		A	R ³	n	W - Y
1		CH ₂ CH ₂	H	1	
2		CH ₂ CH ₂	H	1	
3		CH ₂ CH ₂	H	1	
4		CH ₂ CH ₂	H	1	
5		CH ₂ CH ₂	H	1	
6		CH ₂ CH ₂	H	1	
7		CH ₂ CH ₂	H	1	
8		CH ₂ CH ₂	H	1	
9		CH ₂ CH ₂	H	1	
10		CH ₂ CH ₂	H	1	

Table 1. (continued)

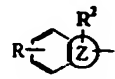
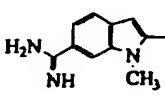
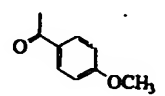
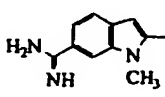
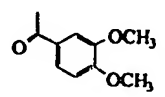
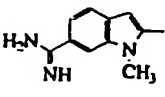
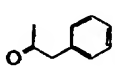
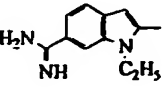
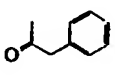
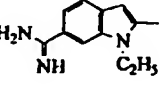
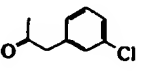
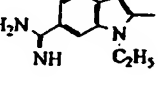
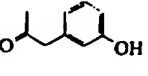
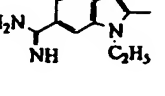
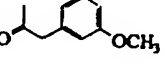
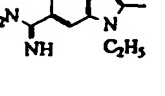
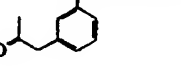
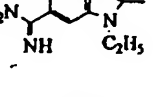
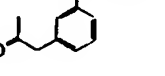
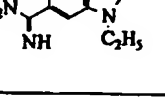
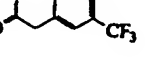
compound No.		A	R ³	n	W - Y
11		CH ₂ CH ₂	H	1	
12		CH ₂ CH ₂	H	1	
13		CH ₂ CH ₂	H	1	
14		CH ₂ CH ₂	H	1	
15		CH ₂ CH ₂	H	1	
16		CH ₂ CH ₂	H	1	
17		CH ₂ CH ₂	H	1	
18		CH ₂ CH ₂	H	1	
19		CH ₂ CH ₂	H	1	
20		CH ₂ CH ₂	H	1	

Table 1. (continued)

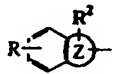
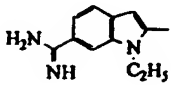
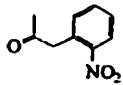
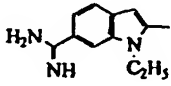
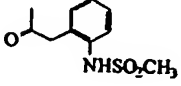
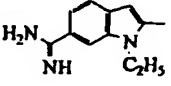
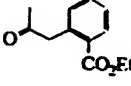
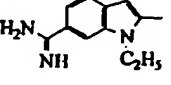
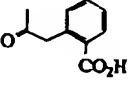
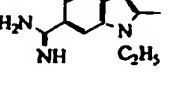
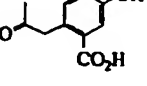
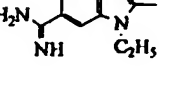
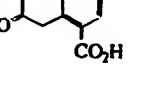
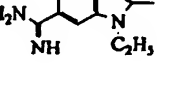
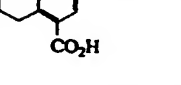
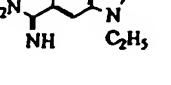
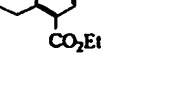
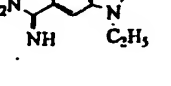
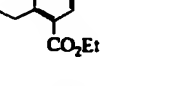
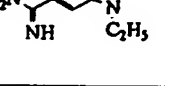

compound No.		A	R ³	n	W - Y
21		CH ₂ CH ₂	H	1	
22		CH ₂ CH ₂	H	1	
23		CH ₂ CH ₂	H	1	
24		CH ₂ CH ₂	H	1	
25		CH ₂ CH ₂	H	1	
26		CH ₂ CH ₂	H	1	
27		CH ₂ CH ₂	H	1	
28		CH ₂ CH ₂	H	1	
29		CH ₂ CH ₂	H	2	
30		CH ₂ CH ₂	H	1	

Table 1. (continued)

5	compound No.		A	R^3	n	W - Y
	31		CH_2CH_2	H	1	
10	32		CH_2CH_2	H	1	
	33		CH_2CH_2	H	1	
15	34		CH_2CH_2	H	1	
	35		CH_2CH_2	H	1	
20	36		CH_2CH_2	H	1	
	37		CH_2CH_2	H	1	
25	38		CH_2CH_2	H	1	
	39		CH_2CH_2	H	1	
30	40		CH_2CH_2	H	1	

Table 1. (continued)

5

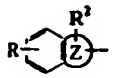
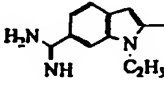
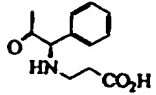
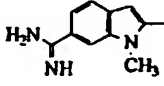
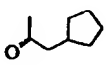
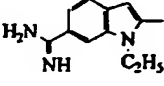
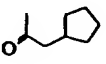
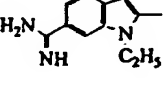
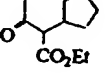
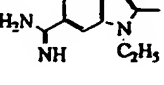
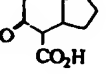
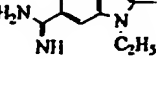
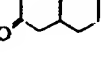
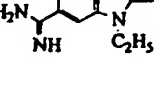
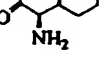
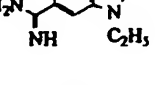
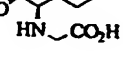
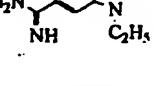
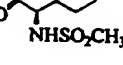
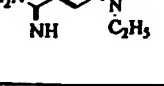

10

15

20

25

30

compound No.		A	R ³	n	W - Y
41		CH ₂ CH ₂	H	1	
42		CH ₂ CH ₂	H	1	
43		CH ₂ CH ₂	H	1	
44		CH ₂ CH ₂	H	1	
45		CH ₂ CH ₂	H	1	
46		CH ₂ CH ₂	H	1	
47		CH ₂ CH ₂	H	1	
48		CH ₂ CH ₂	H	1	
49		CH ₂ CH ₂	H	1	
50		CH ₂ CH ₂	H	1	

35

Table 1. (continued)

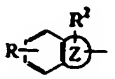
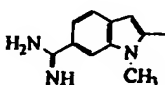
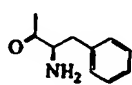
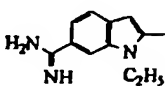
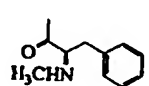
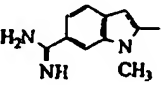
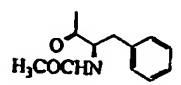
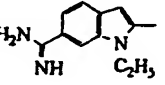
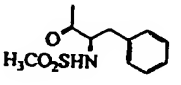
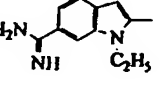
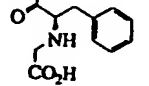
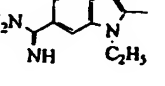
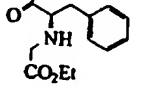
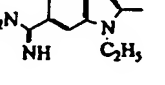
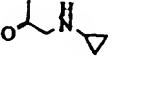
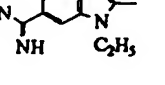
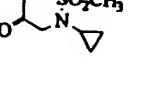
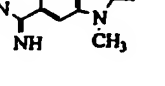
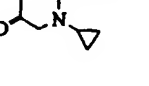
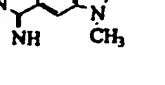
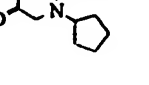
compound No.		A	R ³	n	W - Y
51		CH ₂ CH ₂	H	1	
52		CH ₂ CH ₂	H	1	
53		CH ₂ CH ₂	H	1	
54		CH ₂ CH ₂	H	1	
55		CH ₂ CH ₂	H	1	
56		CH ₂ CH ₂	H	1	
57		CH ₂ CH ₂	H	1	
58		CH ₂ CH ₂	H	1	
59		CH ₂ CH ₂	H	1	
60		CH ₂ CH ₂	H	1	

Table 1. (continued)

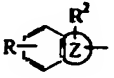
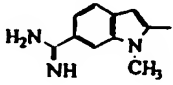
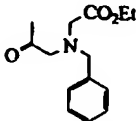
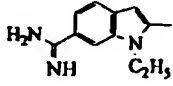
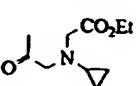
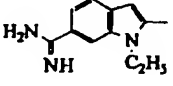
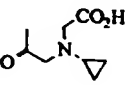
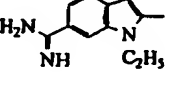
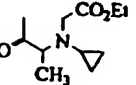
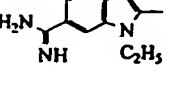
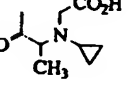
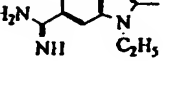
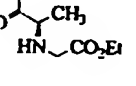
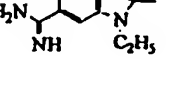
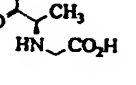
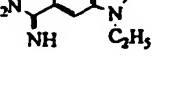
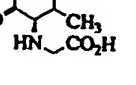
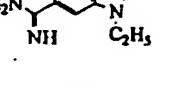
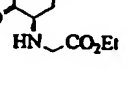
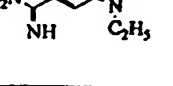
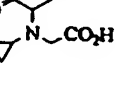
compound No.		A	R ³	n	W - Y
61		CH ₂ CH ₂	H	1	
62		CH ₂ CH ₂	H	1	
63		CH ₂ CH ₂	H	1	
64		CH ₂ CH ₂	H	1	
65		CH ₂ CH ₂	H	1	
66		CH ₂ CH ₂	H	1	
67		CH ₂ CH ₂	H	1	
68		CH ₂ CH ₂	H	1	
69		CH ₂ CH ₂	H	1	
70		CH ₂ CH ₂	H	1	

Table 1. (continued)

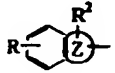
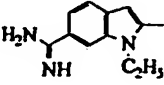
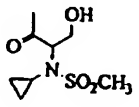
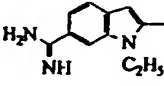
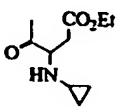
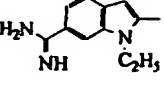
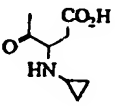
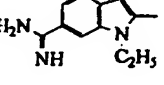
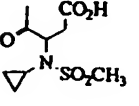
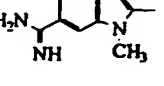
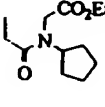
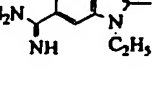
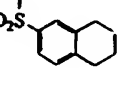
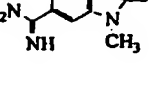
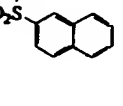
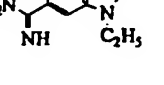
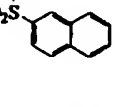
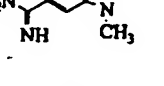
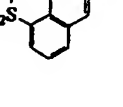
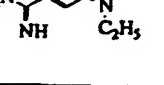
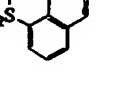
compound No.		A	R ³	n	W - Y
71		CH ₂ CH ₂	H	1	
72		CH ₂ CH ₂	H	1	
73		CH ₂ CH ₂	H	1	
74		CH ₂ CH ₂	H	1	
75		CH ₂ CH ₂	H	1	
76		CH ₂ CH ₂	H	1	
77		CH ₂ CH ₂	H	1	
78		CH ₂ CH ₂	H	2	
79		CH ₂ CH ₂	H	1	
80		CH ₂ CH ₂	H	2	

Table 1. (continued)

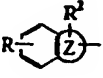
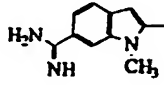

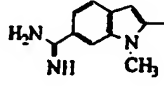
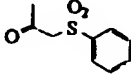
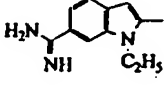

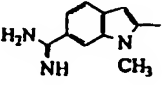

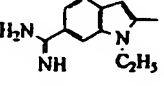

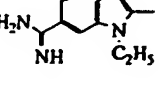

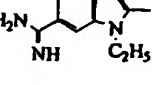

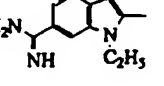

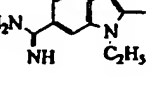

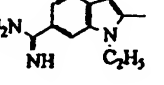

5	compound No.		A	R^3	n	W - Y
	81		CH_2CH_2	H	1	
10	82		CH_2CH_2	H	1	
	83		CH_2CH_2	H	1	
15	84		CH_2CH_2	H	1	
	85		CH_2CH_2	H	0	
20	86		CH_2CH_2	H	1	
	87		CH_2CH_2	H	2	
25	88		CH_2CH_2	H	1	
	89		CH_2CH_2	H	2	
30	90		$CH_2CH_2CH_2$	H	1	

Table 1. (continued)

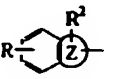
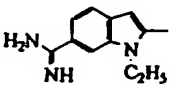
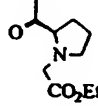
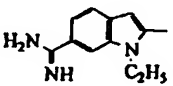
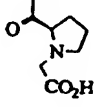
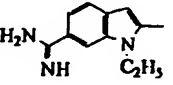
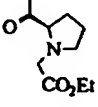
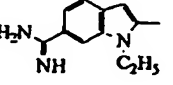
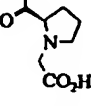
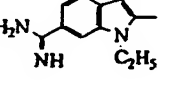
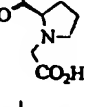
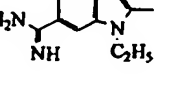
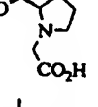
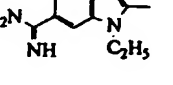
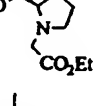
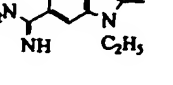
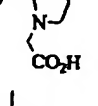
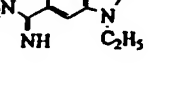
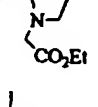
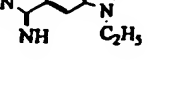
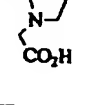
compound No.		A	R ³	n	W - Y
91		$\begin{array}{c} -\text{CH}_2\text{CH}_2- \\ \\ \text{CO}_2\text{Et} \end{array}$	H	1	
92		$\begin{array}{c} -\text{CH}_2\text{CH}_2- \\ \\ \text{CO}_2\text{H} \end{array}$	H	1	
93		$\begin{array}{c} -\text{CH}_2\text{CH}_2- \\ \\ \text{CO}_2\text{Et} \end{array}$	H	1	
94		$\begin{array}{c} -\text{CH}_2\text{CH}_2- \\ \\ \text{CO}_2\text{H} \end{array}$	H	1	
95		$\begin{array}{c} -\text{CH}_2\text{CH}_2- \\ \\ \text{CH}_2\text{OH} \end{array}$	H	1	
96		$\begin{array}{c} -\text{CH}_2\text{CH}_2- \\ \\ \text{CH}_2\text{OH} \end{array}$	H	1	
97		CH_2CH_2	4(S) -CH ₃	1	
98		CH_2CH_2	4(S) -CH ₃	1	
99		CH_2CH_2	4(S) -OCH ₃	1	
100		CH_2CH_2	4(S) -OPh	1	

Table 1. (continued)

5	compound No.		A	R ³	n	W - Y
	101		CH ₂ CH ₂	4(S) -OCH ₂ Ph	1	
10	102		CH ₂ CH ₂	4 -OH	1	
	103		CH ₂ CH ₂	4 -F	1	
15	104		CH ₂ CH ₂	4 -CH ₂ CO ₂ Et	1	
	105		CH ₂ CH ₂	4 -CH ₂ CO ₂ H	1	
20	106		CH ₂ CH ₂	4 -CH ₂ CH ₂ OH	1	
	107		CH ₂ CH ₂	4 -CH ₂ CH ₂ CO ₂ H	1	
25	108		CH ₂ CH ₂	4 -CH ₂ CH ₂ CH ₂ OH	1	
	109		CH ₂ CH ₂	H	1	
30	110		CH ₂ CH ₂	H	1	

Table 1. (continued)

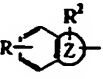
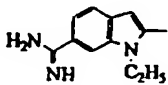
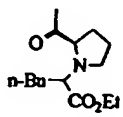
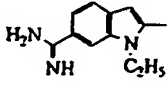
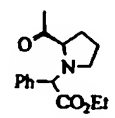
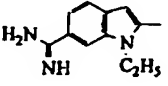
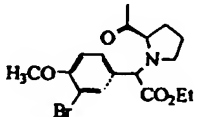
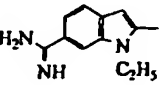
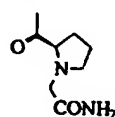
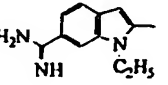
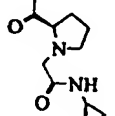
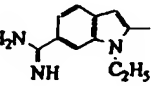
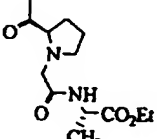
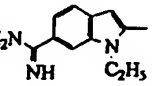
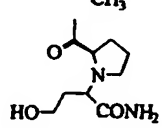
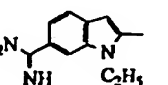
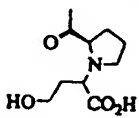
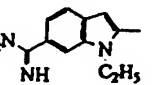
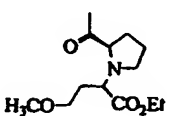
compound No.		A	R ³	n	W - Y
111		CH ₂ CH ₂	H	1	
112		CH ₂ CH ₂	H	1	
113		CH ₂ CH ₂	H	1	
114		CH ₂ CH ₂	H	1	
115		CH ₂ CH ₂	H	1	
116		CH ₂ CH ₂	H	1	
117		CH ₂ CH ₂	H	1	
118		CH ₂ CH ₂	H	1	
119		CH ₂ CH ₂	H	1	

Table 1. (continued)

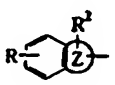
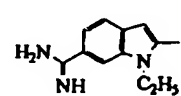
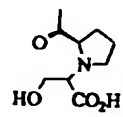
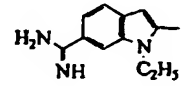
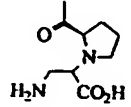
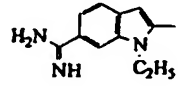
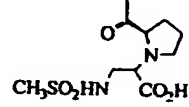
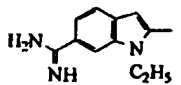
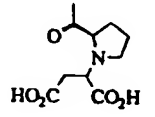
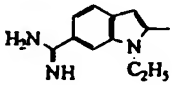
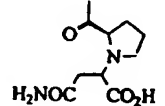
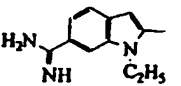
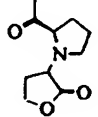
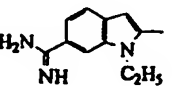
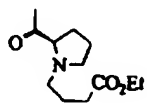
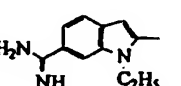
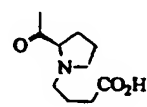
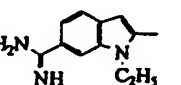
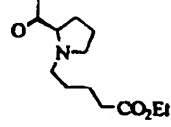
compound No.		A	R ³	n	W - Y
120		CH ₂ CH ₂	H	1	
121		CH ₂ CH ₂	H	1	
122		CH ₂ CH ₂	H	1	
123		CH ₂ CH ₂	H	1	
124		CH ₂ CH ₂	H	1	
125		CH ₂ CH ₂	H	1	
126		CH ₂ CH ₂	H	1	
127		CH ₂ CH ₂	H	1	
128		CH ₂ CH ₂	H	1	

Table 1. (continued)

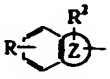
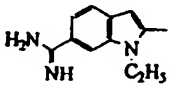
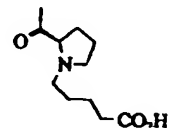
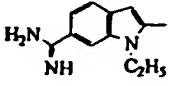
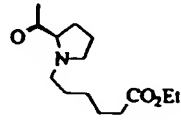
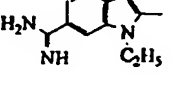
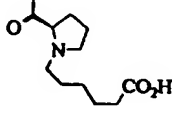
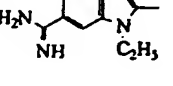
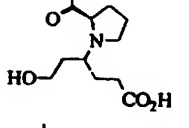
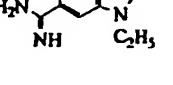
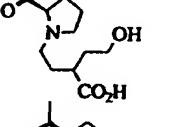
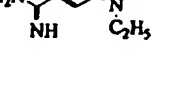
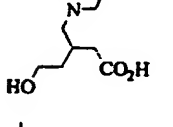
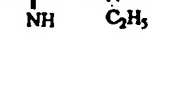
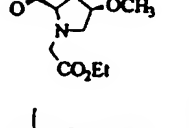
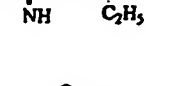
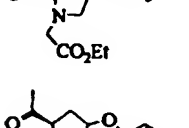
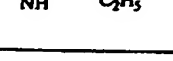
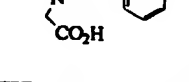
compound No.		A	R ³	n	W - Y
129		CH ₂ CH ₂	H	1	
130		CH ₂ CH ₂	H	1	
131		CH ₂ CH ₂	H	1	
132		CH ₂ CH ₂	H	1	
133		CH ₂ CH ₂	H	1	
134		CH ₂ CH ₂	H	1	
135		CH ₂ CH ₂	H	1	
136		CH ₂ CH ₂	H	2	
137		CH ₂ CH ₂	H	2	

Table 1. (continued)

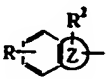
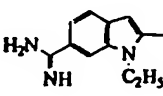
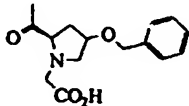
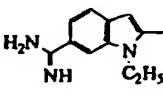
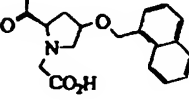
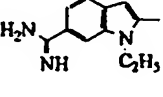
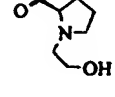
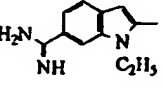
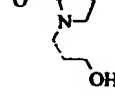
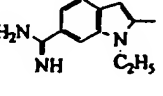
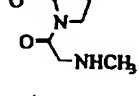
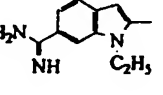
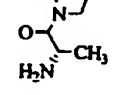
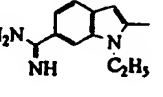
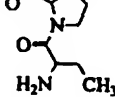
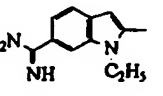
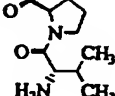
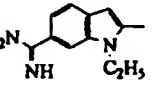
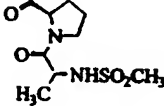
compound No.		A	R ³	n	W - Y
138		CH ₂ CH ₂	H	2	
139		CH ₂ CH ₂	H	2	
140		CH ₂ CH ₂	H	1	
141		CH ₂ CH ₂	H	1	
142		CH ₂ CH ₂	H	1	
143		CH ₂ CH ₂	H	1	
144		CH ₂ CH ₂	H	1	
145		CH ₂ CH ₂	H	1	
146		CH ₂ CH ₂	H	1	

Table 1. (continued)

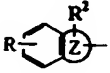
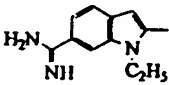
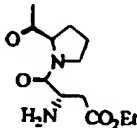
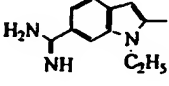
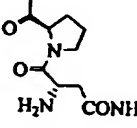
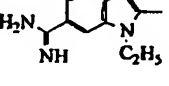
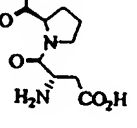
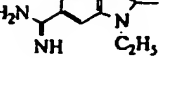
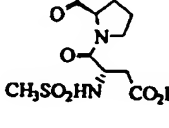
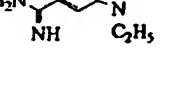
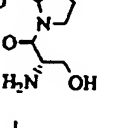
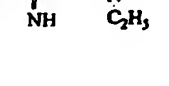
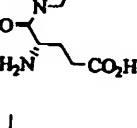
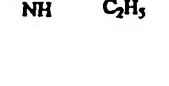
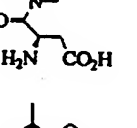

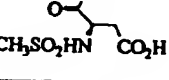
compound No.		A	R ³	n	W - Y
147		CH ₂ CH ₂	H	1	
148		CH ₂ CH ₂	H	1	
149		CH ₂ CH ₂	H	1	
150		CH ₂ CH ₂	H	1	
151		CH ₂ CH ₂	H	1	
152		CH ₂ CH ₂	H	1	
153		CH ₂ CH ₂	H	1	
154		CH ₂ CH ₂	H	1	

Table 1. (continued)

5

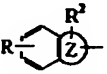
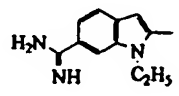
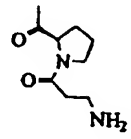
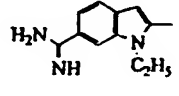
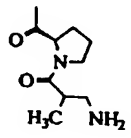
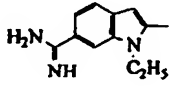
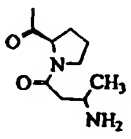
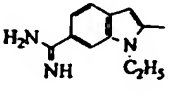
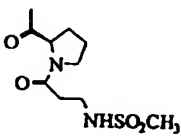
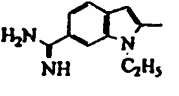
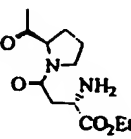
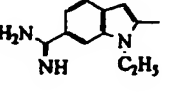
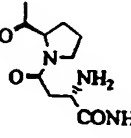
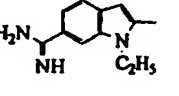
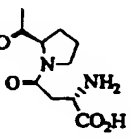
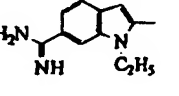
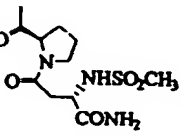
10

15

20

25

30

compound No.		A	R ³	n	W - Y
155		CH ₂ CH ₂	H	1	
156		CH ₂ CH ₂	H	1	
157		CH ₂ CH ₂	H	1	
158		CH ₂ CH ₂	H	1	
159		CH ₂ CH ₂	H	1	
160		CH ₂ CH ₂	H	1	
161		CH ₂ CH ₂	H	1	
162		CH ₂ CH ₂	H	1	

35

Table 1. (continued)

compound No.		A	R^3	n	W - Y
163		CH_2CH_2	H	1	
164		CH_2CH_2	H	1	
165		CH_2CH_2	H	1	
166		CH_2CH_2	H	1	
167		CH_2CH_2	H	1	
168		CH_2CH_2	H	1	
169		CH_2CH_2	H	1	
170		CH_2CH_2	H	1	

Table 1. (continued)

5

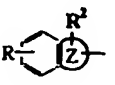
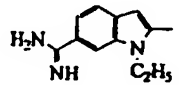
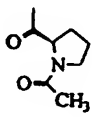
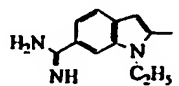
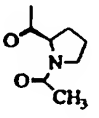
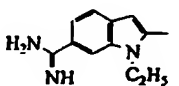
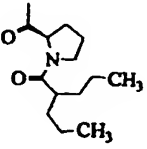
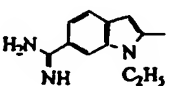
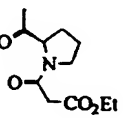
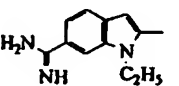
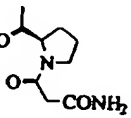
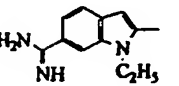
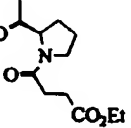
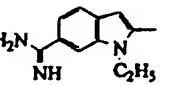
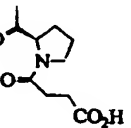
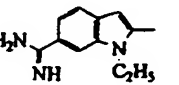
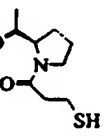
10

15

20

25

30

compound No.		A	R ³	n	W - Y
171		CH ₂ CH ₂	H	1	
172		CH ₂ CH ₂	4 -CH ₂ CO ₂ H	1	
173		CH ₂ CH ₂	H	1	
174		CH ₂ CH ₂	H	1	
175		CH ₂ CH ₂	H	1	
176		CH ₂ CH ₂	H	1	
177		CH ₂ CH ₂	H	1	
178		CH ₂ CH ₂	H	1	

35

Table 1. (continued)


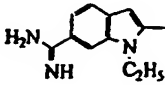
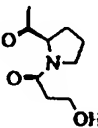
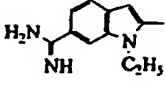
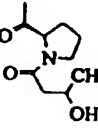
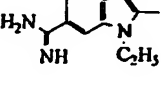
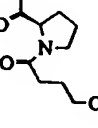
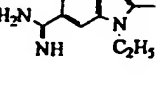
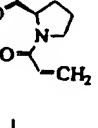
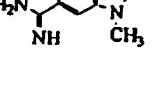
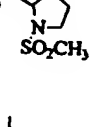
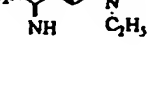
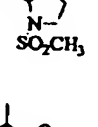
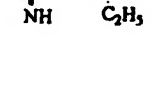

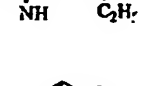
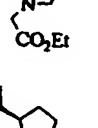
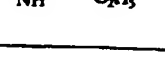

compound No.		A	R ³	n	W - Y
179		CH ₂ CH ₂	H	1	
180		CH ₂ CH ₂	H	1	
181		CH ₂ CH ₂	H	1	
182		CH ₂ CH ₂	H	1	
183		CH ₂ CH ₂	H	1	
184		CH ₂ CH ₂	H	1	
185		CH ₂ CH ₂	4 -CH ₂ CO ₂ H	1	
186		CH ₂ CH ₂	H	1	
187		CH ₂ CH ₂	H	1	

Table 1. (continued)

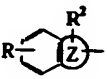
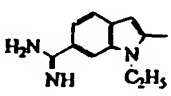
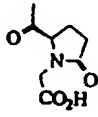
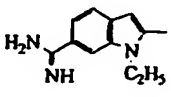

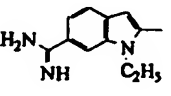
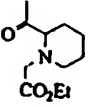
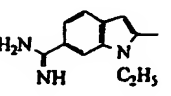
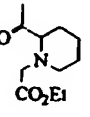
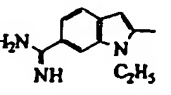
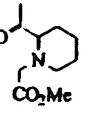
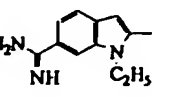
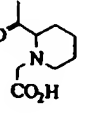
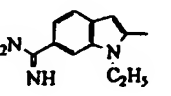
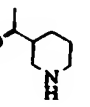
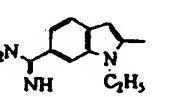

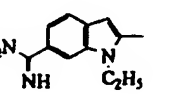
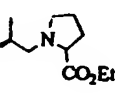
compound No.		A	R ³	n	W - Y
188		CH ₂ CH ₂	H	1	
189		CH ₂ CH ₂	H	1	
190		CH ₂ CH ₂	H	1	
191		CH ₂ CH ₂	H	2	
192		CH ₂ CH ₂	H	1	
193		CH ₂ CH ₂	H	1	
194		CH ₂ CH ₂	H	1	
195		CH ₂ CH ₂	H	1	
196		CH ₂ CH ₂	H	1	

Table 1. (continued)

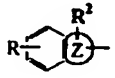
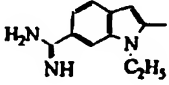
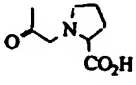
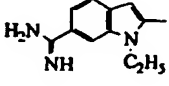
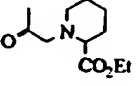
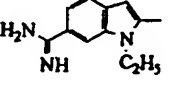
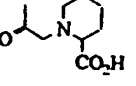
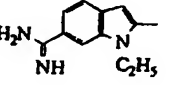

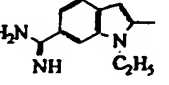
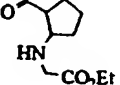
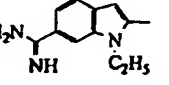
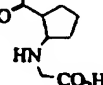
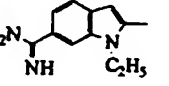
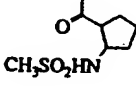
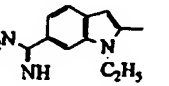
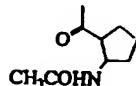
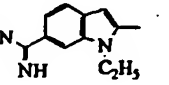
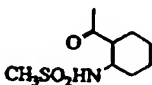
compound No.		A	R ³	n	W - Y
197		CH ₂ CH ₂	H	1	
198		CH ₂ CH ₂	H	1	
199		CH ₂ CH ₂	H	1	
200		CH ₂ CH ₂	H	1	
201		CH ₂ CH ₂	H	1	
202		CH ₂ CH ₂	H	1	
203		CH ₂ CH ₂	H	1	
204		CH ₂ CH ₂	H	1	
205		CH ₂ CH ₂	H	1	

Table 1. (continued)

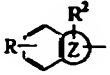
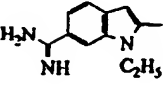
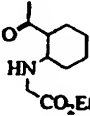
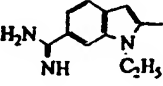
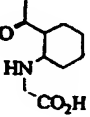
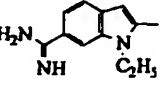

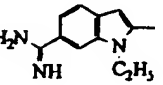
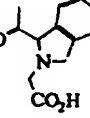
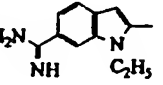

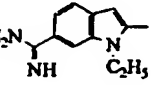
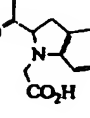
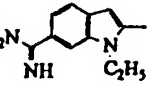
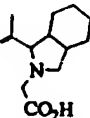
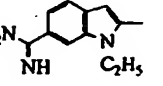
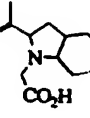
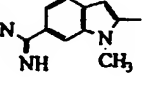

5	compound No.		A	R^3	n	W - Y
	206		CH_2CH_2	H	1	
10	207		CH_2CH_2	H	1	
	208		CH_2CH_2	H	2	
15	209		CH_2CH_2	H	2	
20	210		CH_2CH_2	H	2	
	211		CH_2CH_2	H	2	
25	212		CH_2CH_2	H	2	
	213		CH_2CH_2	H	2	
30	214		CH_2CH_2	H	1	

Table 1. (continued)

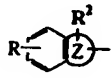
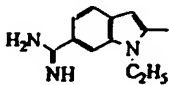
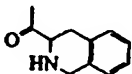
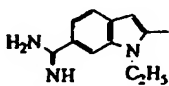
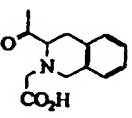
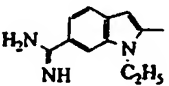
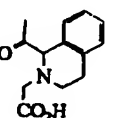
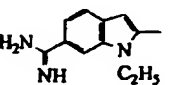
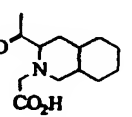
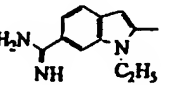
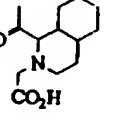
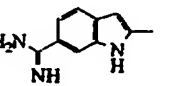
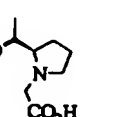
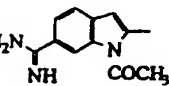
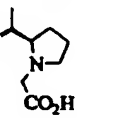
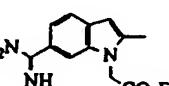
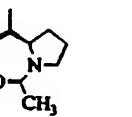
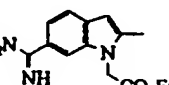
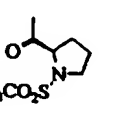
compound No.		A	R^3	n	W - Y
215		CH_2CH_2	H	2	
216		CH_2CH_2	H	2	
217		CH_2CH_2	H	2	
218		CH_2CH_2	H	2	
219		CH_2CH_2	H	2	
220		CH_2CH_2	H	1	
221		CH_2CH_2	H	1	
222		CH_2CH_2	H	1	
223		CH_2CH_2	H	1	

Table 1. (continued)

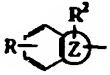
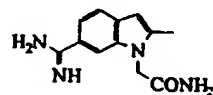
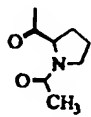
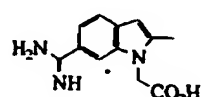
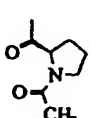
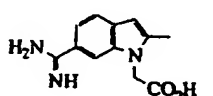
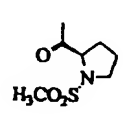
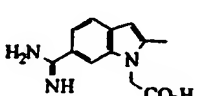
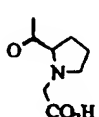
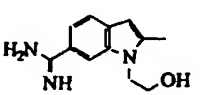
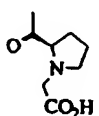
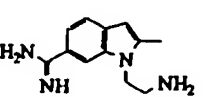
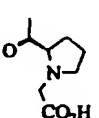
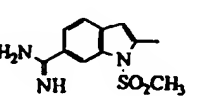
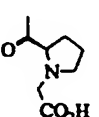
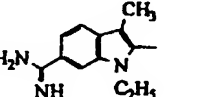
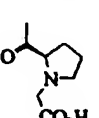
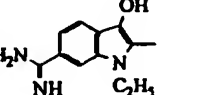
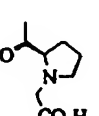
compound No.		A	R ³	n	W - Y
224		CH ₂ CH ₂	H	1	
225		CH ₂ CH ₂	H	1	
226		CH ₂ CH ₂	H	1	
227		CH ₂ CH ₂	H	1	
228		CH ₂ CH ₂	H	1	
229		CH ₂ CH ₂	H	1	
230		CH ₂ CH ₂	H	1	
231		CH ₂ CH ₂	H	1	
232		CH ₂ CH ₂	H	1	

Table 1. (continued)

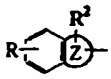
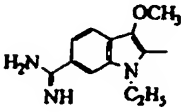
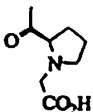
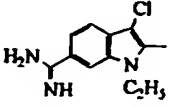
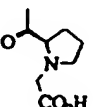
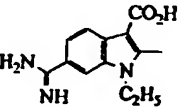
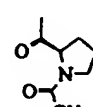
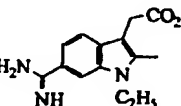
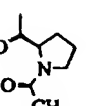
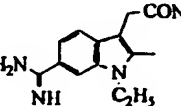
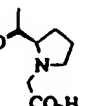
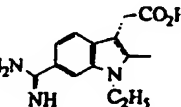
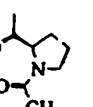
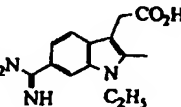
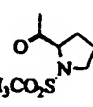
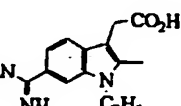
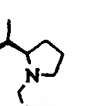
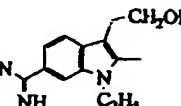
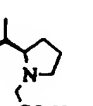
compound No.		A	R ³	n	W - Y
233		CH ₂ CH ₂	H	1	
234		CH ₂ CH ₂	H	1	
235		CH ₂ CH ₂	H	1	
236		CH ₂ CH ₂	H	1	
237		CH ₂ CH ₂	H	1	
238		CH ₂ CH ₂	H	1	
239		CH ₂ CH ₂	H	1	
240		CH ₂ CH ₂	H	1	
241		CH ₂ CH ₂	H	1	

Table 1. (continued)

5

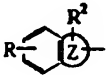
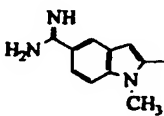
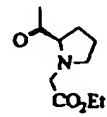
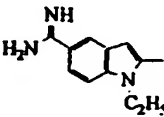
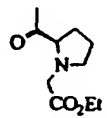
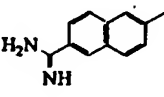
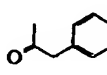
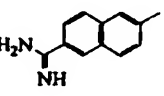
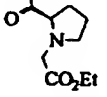
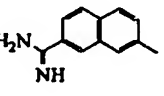
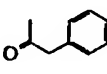
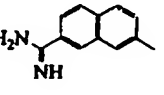
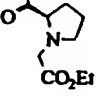
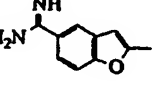
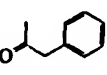
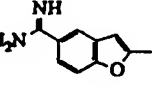
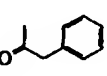
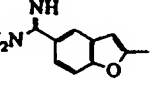
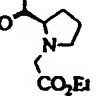
10

15

20

25

30

compound No.		A	R ³	n	W - Y
242		CH ₂ CH ₂	H	1	
243		CH ₂ CH ₂	H	1	
244		CH ₂ CH ₂	H	1	
245		CH ₂ CH ₂	H	1	
246		CH ₂ CH ₂	H	1	
247		CH ₂ CH ₂	H	1	
248		CH ₂ CH ₂	H	1	
249		HC-CH	H	1	
250		CH ₂ CH ₂	H	1	

35

Table 1. (continued)

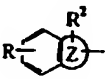
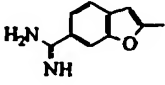
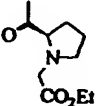
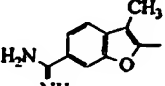
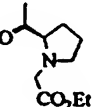
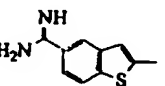
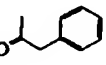
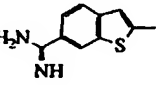
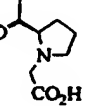
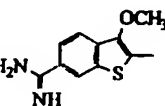
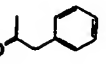
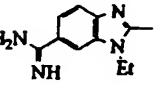
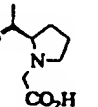
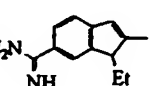
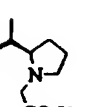
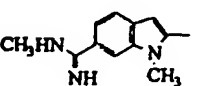
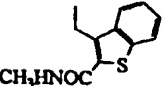
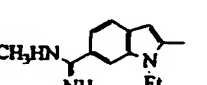
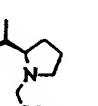
compound No.		A	R ³	n	W - Y
251		CH ₂ CH ₂	H	1	
252		CH ₂ CH ₂	H	1	
253		CH ₂ CH ₂	H	1	
254		CH ₂ CH ₂	H	1	
255		CH ₂ CH ₂	H	1	
256		CH ₂ CH ₂	H	1	
257		CH ₂ CH ₂	H	1	
258		CH ₂ CH ₂	H	1	
259		CH ₂ CH ₂	H	1	

Table 1. (continued)

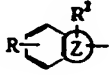
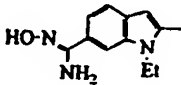
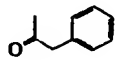
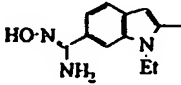
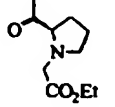
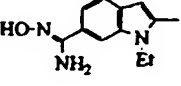
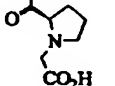
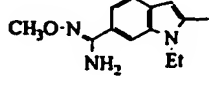
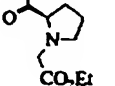
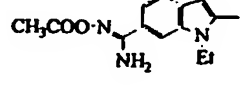
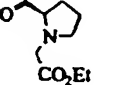
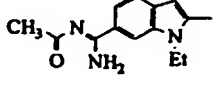
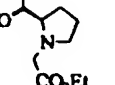
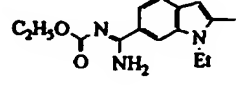
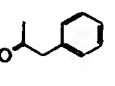
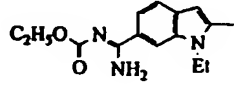
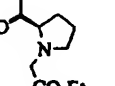
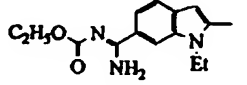
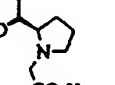
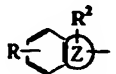
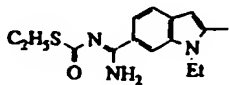
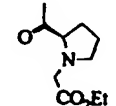
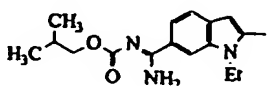
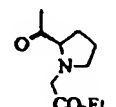
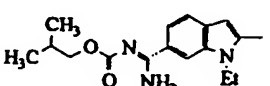
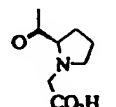
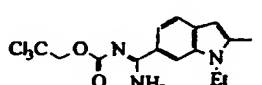
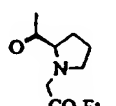
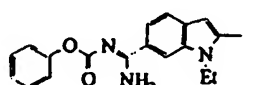
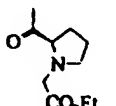
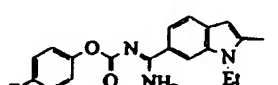
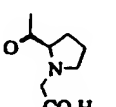
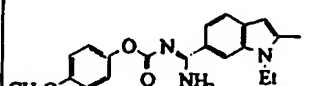
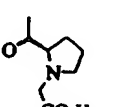
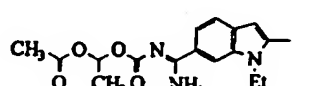
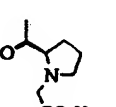
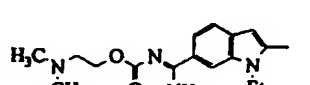
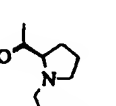
compound No.		A	R ³	n	W - Y
260		CH ₂ CH ₂	H	1	
261		CH ₂ CH ₂	H	1	
262		CH ₂ CH ₂	H	1	
263		CH ₂ CH ₂	H	1	
264		CH ₂ CH ₂	H	1	
265		CH ₂ CH ₂	H	1	
266		CH ₂ CH ₂	H	1	
267		CH ₂ CH ₂	H	1	
268		CH ₂ CH ₂	H	1	

Table 1. (continued)

compound No.		A	R ³	n	W - Y
269		CH ₂ CH ₂	H	1	
270		CH ₂ CH ₂	H	1	
271		CH ₂ CH ₂	H	1	
272		CH ₂ CH ₂	H	1	
273		CH ₂ CH ₂	H	1	
274		CH ₂ CH ₂	H	1	
275		CH ₂ CH ₂	H	1	
276		CH ₂ CH ₂	H	1	
277		CH ₂ CH ₂	H	1	

Specific examples of the particularly preferred compound of formula (I) according to the present invention are as follows:

3-[[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl)methyl]-benzo[b]thiophene-2-carboxamide,

5 3-[[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidin-2-yl)methyl]-benzo[b]thiophene-2-carboxamide,

1-ethyl-2-[2-[(S)-1-[2-(3-chlorophenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

10 2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]benzoic acid,

1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-2-phenylacetyl)pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-((R)-2-methylsulfonylamino-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

15 ethyl 2-[[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenyl]ethyl]amino]acetate,

1-ethyl-2-[2-[(S)-1-((R)-2-(carbamoylmethylamino)-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

20 2-[[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenylethyl]amino]acetic acid,

1-ethyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

ethyl 3-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate,

25 1-ethyl-2-[2-[(S)-1-(2-cyclohexylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

1-ethyl-2-[2-[(S)-1-[2-[cyclopropyl(methylsulfonyl)amino]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,

ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopropylamino]acetate,

ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate,

35 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl

- 2-oxoethyl]cyclopropylamino]acetic acid,
ethyl 4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-cyclopropylamino-4-oxobutanoate,
4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-3-cyclopropylamino-4-oxobutanoic acid,
5 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine,
ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate,
10 ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]acetate,
2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetic acid,
2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]]-(S)-4-methylpyrrolidinyl]carbonyl]pyrrolidinyl]acetic acid,
15 ethyl-2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]propionate,
ethyl-2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]butanoate,
20 ethyl-2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]-2-phenylacetate,
1-ethyl-2-[2-[(S)-1-[(R)-1-(carbamoylmethyl)pyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[(R)-1-[(N-cyclopropylcarbamoyl)methyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
25 ethyl (S)-2-[2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetylamino]propanoate,
1-ethyl-2-[2-[(S)-1-[(R)-1-(1-carbamoyl-3-hydroxypropyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
30 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-hydroxybutanoic acid,
1-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]ethane-1,2-dicarboxylic acid,
1-ethyl-2-[2-[(S)-1-[[1-(2-oxo-3-oxolanyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
35

- ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-
-carbonyl]pyrrolidinyl]butanoate,
4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
-nyl]pyrrolidinyl]butanoic acid,
5 ethyl 5-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-
-carbonyl]pyrrolidinyl]pentanoate,
5-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
-nyl]pyrrolidinyl]pentanoic acid,
ethyl 6-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-
10 -carbonyl]pyrrolidinyl]hexanoate,
6-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
-nyl]pyrrolidinyl]hexanoic acid,
1-ethyl-2-[2-[(S)-1-[(R)-1-[2-(methylamino)acetyl]pyrrolidin-2-yl]carbo-
-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
15 1-ethyl-2-[2-[(S)-1-[(R)-1-[(S)-2-aminopropanoyl]pyrrolidin-2-yl]carbo-
-nyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[(R)-1-(2-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-
pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[(R)-1-[(S)-2-amino-3-methylbutanoyl]pyrrolidin-2-
20 -yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[(R)-1-[(S)-2-(methanesulfonylamino)propanoyl]pyr-
rolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-
-carbonyl]pyrrolidinyl]-(S)-3-amino-4-oxobutanoate,
25 1-ethyl-2-[2-[(S)-1-[(R)-1-[(S)-2-amino-3-carbamoylpropanoyl]pyrroli-
din-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
-nyl]pyrrolidinyl]-(S)-3-amino-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-[(R)-1-(3-aminopropanoyl)pyrrolidin-2-yl]carbonyl]
30 -pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[(R)-1-(3-amino-2-methylpropanoyl)pyrrolidin-2-yl]-
-carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[(R)-1-(3-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-
pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
35 1-ethyl-2-[2-[(S)-1-[(R)-1-[3-[(methanesulfonyl)amino]propanoyl]pyrro-

- lidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-
-carbonyl]pyrrolidinyl]-(S)-2-amino-4-oxobutanoate,
1-ethyl-2-[2-[(S)-1-[(R)-1-((S)-3-amino-3-carbamoylpropanoyl)pyrroli-
5 din-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
-nyl]pyrrolidinyl]-(S)-2-amino-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-[(R)-1-[3-carbamoyl-(S)-3-[(methanesulfonyl)-
amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-
10 carboxamidine,
4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
-nyl]pyrrolidinyl]-(S)-2-[(methanesulfonyl)amino]-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-[(R)-1-(4-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-
pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
15 1-ethyl-2-[2-[(S)-1-[(R)-1-[(2-piperidinyl)carbonyl]pyrrolidin-2-yl]carbo-
-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[(R)-1-(3-piperidinylcarbonyl)pyrrolidin-2-yl]carbo-
-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[(R)-1-[(4-piperidinyl)carbonyl]pyrrolidin-2-yl]carbo-
20 -nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-methyl-2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-
yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-
yl]ethyl]indole-6-carboxamidine,
25 1-ethyl-2-[2-[(S)-1-[(R)-1-(2-propylpentanoyl)pyrrolidin-2-yl]carbonyl]
-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 3-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
-carbonyl]pyrrolidinyl]-3-oxo-propanoate,
1-ethyl-2-[2-[(S)-1-[(R)-1-(2-carbamoylacetyl)pyrrolidin-2-yl]carbonyl]
30 -pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
-carbonyl]pyrrolidinyl]-4-oxobutanoate,
4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
-nyl]pyrrolidinyl]-4-oxobutanoic acid,
35 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-hydroxybutanoyl)pyrrolidin-2-yl]carbonyl]

-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 1-ethyl-2-[2-[(S)-1-[(R)-1-prop-2-enoylpyrrolidin-2-yl]carbonyl]pyrro-
 lidin-2-yl]ethyl]indole-6-carboxamidine,
 1-ethyl-2-[2-[(S)-1-[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]-
 5 pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 1-ethyl-2-[2-[(S)-1-[(R)-1-(carbamoylmethyl)-5-oxopyrrolidin-2-yl]car-
 bonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 methyl-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-
 carbonyl]piperidiny]acetate,
 10 1-ethyl-2-[2-[(S)-1-[(3-piperidiny]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-
 -carboxamidine,
 ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-
 oxoethyl]pyrrolidine-2-carboxylate,
 ethyl 2-[2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-
 15 yl]ethyl]-6-amidinoindolyl]acetate,
 2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-
 1-(carbamoylmethyl)indole-6-carboxamidine, and
 6-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carbox-
 amidine.

20

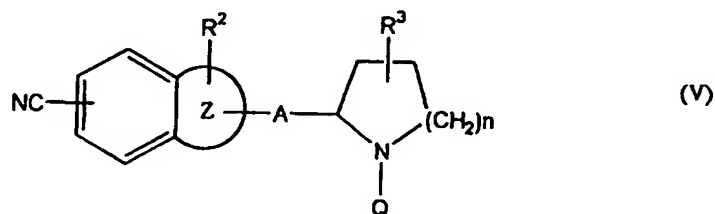
The compound of formula (I) according to the present invention
 can form its pharmaceutically acceptable salt. Such pharmaceutically
 acceptable salts include acid addition salts produced by acid containing
 pharmaceutically acceptable anion which can form a non-toxic salt, for
 25 example, an inorganic acid such as hydrochloric acid, sulfuric acid, nitric
 acid, phosphoric acid, hydrobromic acid, hydroiodic acid, etc., an organic
 carbonic acid such as tartaric acid, formic acid, citric acid, acetic acid,
 trichloroacetic acid or trifluoroacetic acid, gluconic acid, benzoic acid,
 lactic acid, fumaric acid, maleic acid, etc., or sulfonic acid such as
 30 methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naph-
 thalenesulfonic acid, etc.

The purpose of the present invention is also to provide a process
 for preparation of the compound of formula (I).

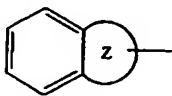
35

According to the method of the present invention, the compound of formula (I) and its salts can be prepared by a process wherein:

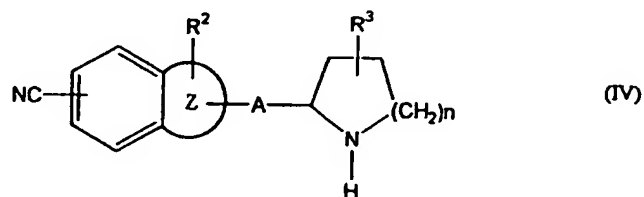
(a) an amino-protecting group of a compound of formula (V):



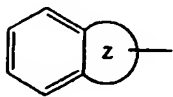
10

wherein , R^2 , R^3 , A and n are defined as in formula (I) and Q represents an amino-protecting group, is removed to obtain a compound of formula (IV):

15



25

wherein , R^2 , R^3 , A and n are defined as in formula (I);

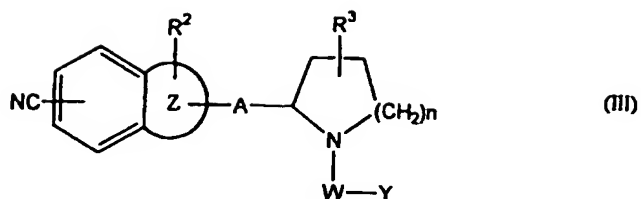
(b) the nitrile compound of formula (IV) thereby obtained is reacted with a compound of formula (VI):



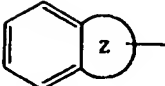
30

wherein Y and W are defined as in formula (I) and D represents hydroxy or halogen, to obtain a compound of formula (III):

35



5

wherein , R^2 , R^3 , A, Y, W and n are defined as in formula (I);

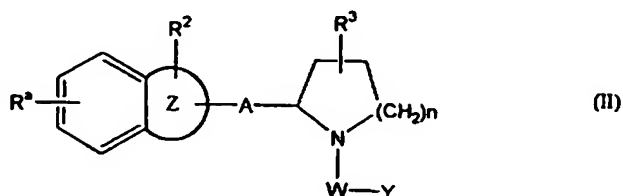
10

(c) the compound of formula (III) is reacted with an alcohol compound of formula (VII):



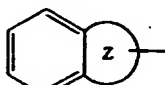
15

wherein R^1 is defined as in formula (I), in the presence of a hydrogen halide to obtain a compound of formula (II):

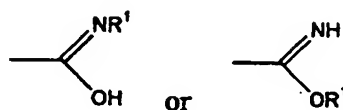


20

25

wherein , R^2 , R^3 , A, Y, W and n are defined as in

formula (I) and R^a is a group of formula



30

wherein R^1 is defined as in formula (I); and

(d) the compound of formula (II) is reacted with ammonia.

35

According to the method of the present invention, in step (a) the amino-protecting group Q is removed from the compound of formula (V) to produce the compound of formula (IV).

In the compound of formula (V), a suitable amino-protecting group includes conventional groups for protecting amino radical, particularly, acyl such as carbamoyl, aliphatic acyl, aromatic acyl, heterocyclic acyl and aliphatic acyl substituted with aromatic group or heterocyclic group which are derived from carboxylic, carbonic, sulfonic and carbamic acids. For example, lower alkanoyl, lower alkylsulfonyl, carbamoyl, N-alkyl-carbamoyl, lower alkoxycarbonyl, lower alkenyloxycarbonyl, alkenoyl, aroyl, arenesulfonyl, aralkanoyl, aralkoxycarbonyl, aryloxyalkanoyl, etc. may be mentioned. Particularly preferred amino-protecting group is t-butoxycarbonyl or benzyloxycarbonyl.

The reaction for removing amino-protecting group of step (a) can be carried out by a conventional method, for example, hydrolysis in the presence of an acid (e.g. an organic acid such as formic acid, acetic acid, propionic acid, trifluoroacetic acid, benzenesulfonic acid or an inorganic acid such as hydrochloric acid, sulfuric acid, phosphoric acid, etc.) or a base (e.g. a hydroxide, hydride, carbonate or bicarbonate of alkali metal or alkaline earth metal such as sodium hydroxide, potassium hydroxide, sodium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, etc.), reduction by using a combination of a metal (e.g. zinc) or a chrome compound (e.g. chromous chloride) and an organic or inorganic acid (e.g. acetic acid, propionic acid, sulfuric acid, phosphoric acid, etc.) or by using hydrogen in the presence of a catalyst (e.g. a metallic catalyst such as palladium, platinum, nickel, etc.), and the like.

In any case, the reaction can generally be carried out in the presence of a solvent which does not adversely influence the reaction. Examples of the solvent which can preferably be used include water, dichloromethane, alcohols such as methanol, ethanol, etc., tetrahydrofuran, 1,4-dioxane, acetone, or a mixture thereof. The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating, preferably at 0°C to 30°C.

In the reaction of step (b), the nitrile compound (IV) produced in step (a) is reacted with the compound of formula (VI) to produce the

compound of formula (III). The reaction of the compound of formula (IV) with the compound of formula (VI) can preferably be carried out in the presence of a reaction-inert solvent. The solvent which can preferably be used for this purpose includes acetone, 1,4-dioxane, acetonitrile, chloroform, dichloromethane, hexamethylphosphoramide, dichloroethane, tetrahydrofuran, ethyl acetate, dimethylsulfoxide, N,N-dimethylformamide, pyridine, or a mixture thereof.

If necessary, the reaction of step (b) can be carried out in the presence of an acid acceptor. The acid acceptor which can preferably be used for this purpose includes an inorganic base, for example, hydroxide, carbonate or bicarbonate of an alkali metal or an alkaline earth metal such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate, etc. or an organic base, for example, triethylamine, trimethylamine, pyridine, N,N-diisopropylethylamine, etc. Particularly, triethylamine or N,N-diisopropylethylamine is most preferably used as the acid acceptor.

The reaction of step (b) can, if appropriate, be carried out in the presence of a condensing agent. The condensing agent which can preferably be used includes a carbodiimide compound such as N,N-diethylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, N,N-dicyclohexylcarbodiimide, etc.

Although the reaction temperature and time are not critical, the reaction is usually carried out under from cooling to heating for 2 to 24 hours, preferably at 0°C to 70°C for 4 to 15 hours.

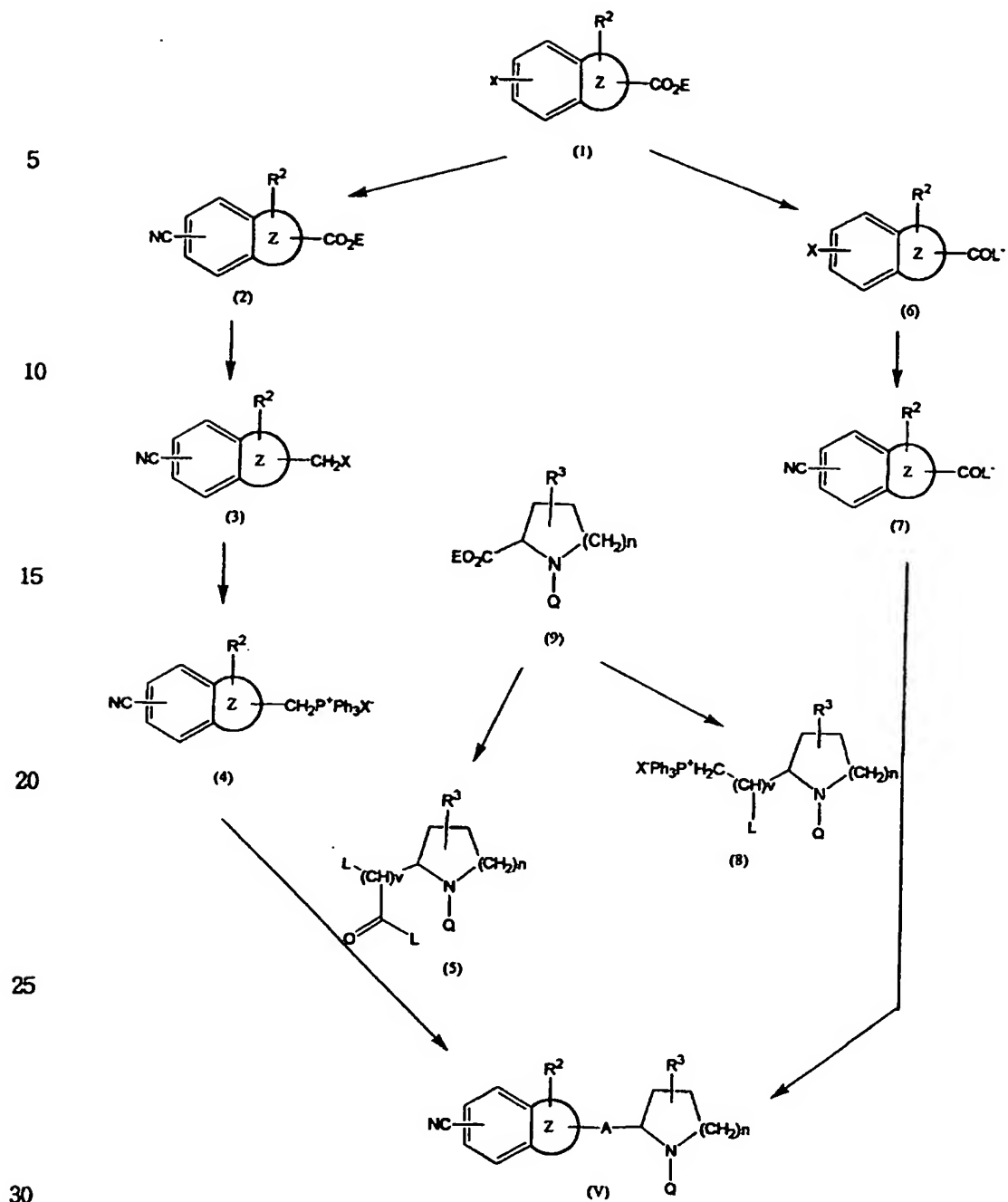
Thereafter, in step (c), the compound of formula (III) produced in step (b) is reacted with the alcohol compound of formula (VII) in the presence of hydrogen halide to produce the compound of formula (II). In this reaction, hydrogen chloride, hydrogen bromide, etc. can be used as hydrogen halide, with hydrogen chloride (HCl) being particularly preferably used. In this reaction, when the alcohol compound of formula (VII) is employed in an excessive amount, it can also be used as a

solvent. If appropriate, this reaction may also be carried out in the presence of a reaction-inert solvent such as chloroform, dichloromethane, benzene, diethyl ether, etc. Although the reaction temperature and time are not critical, the reaction is usually carried out under from cooling to heating for 2 to 48 hours, preferably at 0°C to 30°C for 12 to 24 hours.

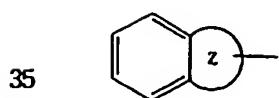
In step (d), the compound of formula (III) produced in step (c) is reacted with ammonia to produce the desired compound of formula (I). This reaction is usually carried out in a solvent, for example, C₁-C₄ alcohol such as ethanol, propanol, etc., aliphatic ether such as diethyl ether, etc., halogenated hydrocarbon such as chloroform, etc., aprotic solvent such as benzene, etc., N,N-dimethylformamide, dimethylsulfoxide, etc., or a mixture thereof. Particularly, C₁-C₄ alcohol solvent such as ethanol is preferably used. Although the reaction temperature and time in this reaction are not critical, the reaction of step (d) is usually carried out under from cooling to heating for 2 to 72 hours, preferably at 0°C to 30°C for 20 to 40 hours.

The compound of formula (I) prepared by the above method according to the present invention can be converted into a salt as mentioned above according to a conventional manner. The compound of formula (I) and its salts thereby produced can be separated and purified by a conventional work-up procedure, for example, column chromatography, recrystallization, etc.

All the compound of formula (V) used as the starting material and the compounds of formulas (II), (III) and (IV) produced as the intermediates in the method for preparation of the compound of formula (I) according to the present invention are novel compounds and therefore, encompassed within the scope of the present invention. The compound of formula (V) used as the starting material in the method of the present invention can be prepared by the two method as shown in the following reaction scheme.



In the above reaction scheme,



, A , R^2 , R^3 and n are defined as in formual (I);

L represents hydrogen, alkyl, alkoxycarbonyl or alkoxycarbonylalkyl and in formula (5) two L groups may be same or different;

E represents hydrogen or lower alkyl;

Q represents an amino-protecting group;

5 X represents halogen; and

v denotes an integer of 0 to 2.

10 The present invention also relates to a thrombin inhibitor composition which contains as an active component a therapeutically effective amount of the compound of formula (I) or its pharmaceutically acceptable salt together with pharmaceutically acceptable carriers. The composition of the present invention exhibits potent thrombin inhibitory activity and can therefore be used as an agent for prevention and treatment of thrombosis.

15

The compound of formula (I) according to the present invention is preferable since it is effective even when orally administered.

20 For clinical purposes, an effective daily dosage of the compound according to the present invention may generally be in the range of 0.1 to 30mg per kg of body weight, and preferably in the range of 0.5 to 10mg per kg of body weight. A dosage suitable for an individual subject can appropriately be determined by a specialist depending on a kind of the compound of formula (I) to be applied, weight, sex, health and nutritional condition of the patient, time and method of administration, excretion rates, a kind of medicines to be administered in combination with the compound of formula (I) and severity of disease.

25

30 The compound of the present invention may be administered either orally or by injection, depending on the dosage and the therapeutic effect desired.

35 Orally administrable solid preparations may be in the form of capsules, tablets, pills, powders and granules, with capsule and tablet preparations being preferable. The tablets and pills can preferably be

5 applied to enteric coating. The solid dosage form can be prepared by intimately mixing the compound of formula (I) according to the present invention with carriers, for example, one or more inert diluents such as sucrose, lactose, starch, etc., lubricants such as magnesium stearate, disintegrating agents, binders, etc.

10 As mentioned above, the compositions containing the compound of formula (I) according to the present invention are characterized by their superior effect even when orally administered. These has been demonstrated through pharmacokinetic experiments using rats and dogs as the test animals, in which the active compound is shown to be retained in blood for a long time when the composition is orally administered. The compound of the present invention is, therefore, more useful than thrombin inhibitors disclosed in the prior art because it can
15 be effectively used in the form of an oral preparation.

The composition containing the compound of formula (I) according to the present invention can also be formulated in the form of an injectable preparation, for example, as a sterilized injectable aqueous or
20 oily suspension using suitable dispersing agents, wetting agents or suspending agents. Aqueous solvents which can be used for this purpose include water, Ringer's solution or isotonic NaCl solution. Sterilized fixing oils may also be used as a solvent or suspending agent. Non-irritable fixing oils including mono-, di-glycerides can be used for
25 this purpose, and fatty acids such as oleic acid may be used in injectable preparations.

In addition, according to the results of experiment, it has been identified that the compound of formula (I) according to the present
30 invention exhibits potent thrombin inhibitory activity without acute toxicity in mammals, such as rats and dogs.

Although the present invention is specifically illustrated by the following examples, the present invention is not in any manner limited by
35 these examples.

Example 1 : Synthesis of 1-ethyl-2-[2-((S)-1-benzylpyrrolidin-2-yl)ethyl]indole-6-carbonitrile (Compound 1)

a) Synthesis of 4-methyl-3-nitrobenzenecarbonitrile:

5

In a 250ml flask, 10g of 4-methylbenzenecarbonitrile was dissolved in 30ml of concentrated sulfuric acid and then cooled to 0°C. 7ml of nitric acid mixed with 10ml of concentrated sulfuric acid was slowly added thereto over one hour at -2°C to 0°C. The reaction solution was poured into ice water and then stirred. The resulting precipitate was filtered, washed three times with water and then dried. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 11.2g of the title compound as a white solid.

15

¹H NMR(CDCl₃, ppm) : δ 8.30(s, 1H), 7.80(d, 1H), 7.53(d, 1H), 2.7(s, 3H)

b) Synthesis of ethyl 3-(4-cyano-2-nitrophenyl)-2-sodiumprop-2-enoate:

20

To a 500ml flask, 2.51g of sodium and 60ml of tetrahydrofuran were added and 30ml of ethanol was then added thereto. The mixture was stirred at room temperature until sodium was completely dissolved. A solution of 14.8ml of diethyl oxalate in tetrahydrofuran was slowly added thereto and the mixture was stirred for 10 minutes at room temperature. 16g of 4-methyl-3-nitrobenzenecarbonitrile dissolved in tetrahydrofuran was added thereto and the mixture was stirred for 18 hours at room temperature. The reaction solution was evaporated and ether was added to the residue. The resulting precipitate was filtered, washed three times with ether and then dried to obtain 26.4g of the title compound as a brown solid.

25

30

c) Synthesis of ethyl 6-cyanoindole-2-carboxylate:

35

26g of ethyl 3-(4-cyano-2-nitrophenyl)-2-sodiumprop-2-enoate

and 59.8g of Zn were introduced into a 500ml flask and 200ml of acetic acid was added thereto. The mixture was stirred for 2 hours at room temperature and then for 4 hours at 60~70°C. The reaction solution was evaporated, and the residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 4.16g of the title compound as a yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.82(m, 2H), 7.42(d, 1H), 7.29(s, 1H), 4.49(m, 2H), 1.47(t, 3H)

d) Synthesis of ethyl 6-cyano-1-ethylindole-2-carboxylate:

In a 1 l flask, 23.5g of ethyl 6-cyanoindole-2-carboxylate was dissolved in 300ml of dimethylformamide, and 6.6g of 60% NaH was slowly added thereto at 0°C. 17.6ml of iodoethane was then added thereto at -10~0°C and the mixture was stirred for 2 hours at room temperature. The reaction solution was cooled and, after adding ice, diluted with water and then extracted three times with ethyl acetate. The organic extracts were combined, dried over MgSO₄ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 26.2g of the title compound as a yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.77(m, 2H), 7.34(m, 2H), 4.64(m, 2H), 4.42(m, 2H), 1.43(m, 6H)

e) Synthesis of 1-ethyl-2-(hydroxymethyl)indole-6-carbonitrile:

In a 1 l flask, 26.27g of ethyl 6-cyano-1-ethylindole-2-carboxylate and 0.91g of sodium bicarbonate were dissolved with 300ml of tetrahydrofuran and then cooled to 0°C. To this mixture was added CaI₂ · H₂O and then slowly added NaBH₄. The reaction mixture was stirred while slowly warming from 0°C to room temperature with stirring.

After examined by TLC, ice and a catalytic amount of acetic acid were added thereto at 0°C and the mixture was stirred. The reaction solution was evaporated to remove tetrahydrofuran, and the residue was diluted with water and extracted three times with ethyl acetate. The organic
5 extracts were combined, dried over MgSO₄ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:2)]. The fractions containing the desired product were combined and then evaporated to obtain 18.2g of the title compound as a white solid.

10 ¹H NMR(CDCl₃, ppm) : δ 7.63(m, 2H), 7.26(m, 1H), 6.43(s, 1H), 4.83(s, 2H), 4.29(m, 2H), 1.41(t, 3H)

15 f) Synthesis of 6-cyano-1-ethylindole-2-methyl triphenylphosphonium bromide:

In a 500ml flask, 18.2g of 1-ethyl-2-(hydroxymethyl)indole-6-carbonitrile was dissolved in 200ml of dichloromethane and then cooled to 0°C. 3.45ml of PBr₃ was slowly added thereto, and the mixture was
20 stirred for 4 hours at room temperature. dichloromethane was then added and the reaction mixture was washed with aqueous Na₂CO₃ solution, diluted with water and then extracted three times with dichloromethane. The organic extracts were combined, dried over MgSO₄ and then evaporated to obtain 6-cyano-1-ethyl-2-bromomethyl
25 indole. The resulting product was dissolved in 200ml of toluene and 30.9g of triphenylphosphine was added thereto. The mixture was stirred for 10 hours at refluxing temperature and then cooled to room temperature. To this reaction solution was added diethyl ether, and the resulting precipitate was then filtered, washed several times with diethyl
30 ether and dried to obtain 29g of the title compound as a pale brown solid.

g) Synthesis of (S)-methyl pyrrolidine-2-carboxylate:

35 In a 250ml flask, 10g of L-proline was dissolved in 150ml of methanol, and HCl gas was bubbled therein at 0°C for 2 hours to saturate

the solution. The reaction solution was then stirred for 5 hours at room temperature and evaporated to remove the solvent, thereby obtain 11.2g of the title compound as a colorless oil.

5 ^1H NMR(CDCl_3 , ppm) : δ 4.50(m, 1H), 3.86(s, 3H), 3.52(m, 2H), 2.48(m, 1H), 2.20(m, 3H)
MS : 130(M+1) $^+$, 116

10 h) Synthesis of 1-tert-butyl-(S)-2-(methoxycarbonyl)pyrrolidine carboxylate:

In a 500ml flask, 11.2g of (S)-methyl pyrrolidine-2-carboxylate was dissolved in 200ml of dichloromethane and 12ml of triethylamine was added, and the mixture was then stirred for 5 minutes. 20.9g of
15 $(\text{Boc})_2\text{O}$ dissolved in dichloromethane was added thereto at 0°C, and the reaction mixture was stirred for 4 hours at room temperature, diluted with water and extracted three times with dichloromethane. The organic extracts were combined, dried over MgSO_4 and then evaporated to obtain 19.9g of the title compound as a colorless oil.

20 ^1H NMR($\text{MeOH}-d_4$, ppm) : δ 4.20(m, 1H), 3.68(s, 3H), 3.37(m, 2H), 2.22(m, 1H), 1.89(m, 3H), 1.41(m, 9H)

i) Synthesis of 1-tert-butyl-(S)-2-formylpyrrolidine carboxylate:

25 In a 500ml flask, 9.8g of 1-tert-butyl-(S)-2-(methoxycarbonyl)-pyrrolidine carboxylate was dissolved in 200ml of toluene and 85.5ml of DIBAL-H(diisobutylaluminum hydride, 1.0M in toluene) was slowly added over 1.5 hour while cooling to -78°C. 15ml of methanol was then added
30 thereto, and the mixture was stirred for 30 minutes at room temperature. To this solution, aqueous solution of Rochell's salt (potassium sodium tartrate tetrahydrate) was added, and the reaction solution was stirred for about one hour at room temperature and then extracted with dichloromethane. The organic extracts were combined, dried over
35 MgSO_4 and evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions

containing the desired product were combined and then evaporated to obtain 8g of the title compound as a colorless oil.

- 5 j) Synthesis of 1-tert-butyl-(S)-2-[2-(6-cyano-1-ethylindol-2-yl)vinyl]-pyrrolidine carboxylate:

In a 500ml flask, 17.4g of 6-cyano-1-ethylindole-2-methyl triphenylphosphonium bromide and 6.6g of 1-tert-butyl-(S)-2-formylpyrrolidine carboxylate were dissolved in a mixed solvent of tetrahydrofuran/ethanol (1:1), and 6.4ml of 1,8-diazabicyclo[5.4.0]undec-7-ene was added thereto. The reaction solution was stirred for 15 hours at room temperature and evaporated to remove the solvent. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 7.8g of the title compound as a yellow oil.

- k) Synthesis of 1-tert-butyl-(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidine carboxylate:

20 In a 500ml flask, 13g of 1-tert-butyl-(S)-2-[2-(6-cyano-1-ethylindol-2-yl)vinyl]pyrrolidine carboxylate was dissolved in 250ml of ethanol, and 4g of 10% palladium on activated carbon was slowly added thereto. Hydrogen gas was bubbled into the reaction solution and the mixture was stirred for 3 hours at room temperature. The reaction solution was filtered through a celite and evaporated to remove the solvent. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 12g of the title compound as a brown oil.

30 ^1H NMR(CDCl_3 , ppm) : δ 7.60(m, 2H), 7.28(m, 1H), 6.36(s, 1H), 4.15(m, 2H), 3.94(m, 1H), 3.72(m, 1H), 3.38(m, 3H), 2.76(t, 2H), 1.46(s, H), 1.39(m, 3H)

- 35 l) Synthesis of 1-ethyl-2-[2-((S)-pyrrolidin-2-yl)ethyl]indole-6-carbonitrile (Compound I-a):

In a 250ml flask, 3.7g of 1-tert-butyl-(S)-2-[2-(6-cyano-1-ethyl-indol-2-yl)ethyl]pyrrolidine carboxylate was dissolved in 100ml of dichloromethane, and 18.2ml of trifluoroacetic acid was slowly added thereto at 0°C. The reaction mixture was stirred for about 2 hours at room temperature, and after adding dichloromethane, then diluted with water and washed three times with saturated aqueous NaHCO₃ solution. The aqueous layer was extracted three times with dichloromethane. The organic extracts were combined, dried over MgSO₄ and then evaporated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(3:1)]. The fractions containing the desired product were combined and then evaporated to obtain 2.2g of the title compound as a pale yellow foam.

¹H NMR(CDCl₃, ppm) : δ 7.48(m, 2H), 7.28(m, 1H), 6.33(s, 1H), 4.03(m, 2H), 3.58(m, 1H), 3.27(m, 2H), 2.85(m, 2H), 2.35(m, 1H), 2.11(m, 3H), 2.00(m, 1H), 1.80(m, 1H), 1.27(t, 3H)

m) Synthesis of 1-ethyl-2-[2-((S)-1-benzylpyrrolidin-2-yl)ethyl]indole-6-carbonitrile:

66mg of the compound I-a obtained in the above l) was dissolved in dichloromethane and then cooled to 0°C. To this solution, 46μl of triethylamine was added and 38μl of benzyl chloride was then slowly added. The reaction mixture was stirred for 4 hours at room temperature and then diluted with excess of dichloromethane. The organic layer was washed with water, dried over MgSO₄ and filtered under reduced pressure. The filtrate was concentrated and the concentrate was purified with silica gel column chromatography [eluent: dichloromethane/methanol(10:1)]. The fractions containing the desired product were combined and evaporated to obtain 39mg of the title compound.

n) Synthesis of 1-ethyl-2-[2-((S)-1-benzylpyrrolidin-2-yl)ethyl]indole-6-carboxamide:

39mg of 1-ethyl-2-[2-((S)-1-benzylpyrrolidin-2-yl)ethyl]indole-6-

carbonitrile was dissolved in ethanol and cooled to 0°C. HCl gas was bubbled for 45 minutes into the solution, and the reaction solution was stirred at room temperature overnight and concentrated under reduced pressure to remove the solvent. The residue was dissolved in ethanol and ammonia gas was bubbled into the solution for one hour at 0°C. The reaction solution was stirred overnight at room temperature and then distilled under reduced pressure. The residue was purified with column chromatography [eluent: dichloromethane/methanol(4:1)] on NH-DM1020 silica to obtain 32mg of the title compound a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.93(s, 1H), 7.66(d, 1H, J=8.41Hz), 7.44(d, 1H, J=8.41Hz), 7.34-7.27(m, 5H), 6.40(s, 1H), 4.28(q, 2H), 4.07(d, 1H), 2.95-2.88(m, 3H), 2.60(m, 1H), 2.31-1.90(m, 4H), 1.80-1.55(m, 5H), 1.40(t, 3H, J=7.21Hz)

Example 2 : Synthesis of ethyl 2-[(S)-2-[2-(6-amidino-1-methyl-indol-2-yl)ethyl]pyrrolidinyl]-2-phenylacetate (Compound 2)

a) Synthesis of 6-cyano-1-methylindole-2-methyl triphenyl phosphonium bromide:

The reaction was carried out according to the same procedure as Examples 1-a) through 1-f), except that iodomethane was used in place of iodoethane in Example 1-d), to obtain 15g of the title compound as a pale brown solid.

¹H NMR(DMSO-d₆, ppm) : δ 8.00(s, 1H), 7.92(m, 3H), 7.84-7.68(m, 12H), 7.62(d, 1H, J=8.24Hz), 7.35(d, 1H, J=8.24Hz), 6.28(s, 1H), 5.57(d, 2H, J=15.2Hz), 3.19(s, 3H)

b) Synthesis of 1-methyl-2-[2-((S)-pyrrolidin-2-yl)ethyl]-indole-6-carbonitrile (Compound I-b):

6-Cyano-1-methylindole-2-methyl triphenylphosphonium bromide obtained in the above a) was reacted according to the same procedure as Example 1-l) to obtain 6.4g of the title compound as a pale yellow foam.

¹H NMR(MeOH-d₄, ppm) : δ 7.83(s, 1H), 7.62(d, 1H, J=8.24Hz), 7.30(d, 1H, J=8.24Hz), 6.47(s, 1H), 3.80(s, 3H), 3.64(m, 1H), 3.32(m, 2H), 3.00(m, 2H), 2.41-1.98(m, 5H), 1.80(m, 1H)

- 5 c) Synthesis of ethyl 2-[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]-pyrrolidiny]-2-phenylacetate:

90mg of the compound I-b obtained in the above b) and 86mg of ethyl-2-bromo-2-phenylacetate were treated according to the same
10 procedure as Example 1-m) to obtain 85mg of the title compound as a pale yellow solid.

- d) Synthesis of ethyl 2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]-pyrrolidiny]-2-phenylacetate:

15 81mg of ethyl 2-[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]-pyrrolidiny]-2-phenylacetate obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 19mg of the title compound as a pale yellow solid.

20 ¹H NMR(MeOH-d₄, ppm) : δ 7.82(d, 1H, J=11.06Hz), 7.52(d, 1H, J=8.1Hz), 7.32(m, 3H), 7.19(m, 3H), 6.10(s, 1H), 4.36(s, 1H), 4.00(m, 2H), 1.95(m, 2H), 1.74-1.45(m, 6H), 1.06(m, 3H)

25 Example 3 : Synthesis of 2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidiny]-2-phenylacetic acid (Compound 3)

13mg of ethyl 2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]-pyrrolidiny]-2-phenylacetate obtained in Example 2 was dissolved in 5ml of 35% hydrochloric acid solution, and the resulting solution was heated
30 to 60°C and stirred for 1.5 hours, and then stirred at room temperature overnight. The reaction solvent was removed by distillation under reduced pressure. The residue was purified with column chromatography [eluent: dichloromethane/methanol(2:3)] on NH-DM1020 silica. The fractions containing the desired product were combined and then
35 distilled under reduced pressure to obtain 6.2mg of the title compound as a

pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.75(s, 1H), 7.59-7.51(m, 1H), 7.31-7.20(m, 5H), 6.33(s, 1H), 4.13(s, 1H), 3.74(s, 3H), 3.61(s, 1H), 2.98(m, 2H), 2.89(m, 3H), 2.75(m, 2H), 2.40(m, 1H), 2.35-2.05(m, 3H), 1.80-1.77(m, 6H)

Example 4 : Synthesis of 1-methyl-2-[2-[(S)-1-(1-naphthylmethyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 4)

a) Synthesis of 1-methyl-2-[2-[(S)-1-(1-naphthylmethyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

89mg of the compound I-b obtained in Example 2-b), 127mg of 1-naphthalenemethanol and 148mg of triphenylphosphine were dissolved in chloroform, and 104μl of DEAD(diethylazodicarboxylate) was slowly added thereto while stirring at room temperature. The mixture was stirred at room temperature overnight and distilled under reduced pressure to remove the solvent. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(1:1)]. The fraction containing the desired product was distilled under reduced pressure to obtain 33mg of the title compound.

b) Synthesis of 1-methyl-2-[2-[(S)-1-(1-naphthylmethyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

30mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 11mg of the title compound as a yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 8.20(m, 1H), 7.76(m, 2H), 7.68(d, 1H, J=8.66Hz), 7.52(d, 1H, J=8.21Hz), 7.37-7.22(m, 5H), 6.21(s, 1H), 4.37(d, 1H), 3.65(m, 1H), 3.55(m, 1H), 2.10-1.90(m, 5H), 1.66-1.61(m, 6H)

Example 5 : Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylmethyl)-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 5)

a) Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylmethyl)pyrrolidin-2-yl]-ethyl]indole-6-carbonitrile:

In a 25ml flask, 70mg of the compound 1-b obtained in Example 2-b) and 54mg of 2-naphthalenemethanol were dissolved in 5ml of tetrahydrofuran. To the resulting solution, 105mg of triphenylphosphine was added and 0.08ml of DEAD was then added at room temperature. The mixture was stirred for about 40 hours at room temperature and then evaporated to remove the solvent. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/methanol(10:1)]. The fractions containing the desired product were combined and then evaporated to obtain 20mg of the title compound as a pale yellow solid.

^1H NMR(MeOH- d_4 , ppm) : δ 7.81(m, 1H), 7.69(m, 4H), 7.52(m, 1H), 7.47(m, 3H), 7.28(d, 1H), 6.30(s, 1H), 4.14(d, 1H), 3.60(s, 3H), 3.57(d, 1H), 2.99(m, 1H), 2.88(m, 1H), 2.76(m, 1H), 2.63(m, 1H), 2.40(m, 1H), 2.14(m, 2H), 1.79(m, 4H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylmethyl)pyrrolidin-2-yl]-ethyl]indole-6-carboxamidine:

18mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 10mg of the title compound as a pale yellow solid.

^1H NMR(MeOH- d_4 , ppm) : δ 7.76-7.62(m, 5H), 7.51(d, 1H), 7.35(m, 4H), 6.24(s, 1H), 4.06(d, 1H), 3.60(s, 3H), 3.45(d, 1H), 2.86(m, 1H), 2.72(m, 2H), 2.53(m, 1H), 2.27(m, 1H), 2.04(m, 2H), 1.69(m, 4H)

Example 6 : Synthesis of 1-methyl-2-[2-[(S)-1-(benzo[d][1,3-dioxolen-5-yl-methyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 6)

a) Synthesis of 1-methyl-2-[2-[(S)-1-(benzo[d]1,3-dioxolen-5-ylmethyl)-pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

5 In a 100ml flask, 100mg of the compound I-b obtained in Example 2-b) and 66mg of piperonyl alcohol were reacted according to the same procedure as Example 5-a) to obtain 40mg of the title compound as a pale yellow solid.

10 ¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.31(d, 1H), 6.83(s, 1H), 6.72(m, 2H), 6.32(d, 1H), 5.91(s, 2H), 3.92(d, 1H), 3.69(s, 3H), 3.21(d, 1H), 2.98(m, 1H), 2.86-2.74(m, 2H), 2.54(m, 1H), 2.19(m, 1H), 2.03(m, 2H), 1.77(m, 3H), 1.73(m, 1H)

15 b) Synthesis of 1-methyl-2-[2-[(S)-1-(benzo[d]1,3-dioxolen-5-ylmethyl)-pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

40mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 16mg of the title compound as a pale yellow solid.

20 ¹H NMR(CDCl₃, ppm) : δ 7.89(m, 1H), 7.39(m, 2H), 6.79(s, 1H), 6.69(m, 2H), 6.14(s, 1H), 5.89(s, 2H), 3.88(d, 1H), 3.57(s, 3H), 3.11(d, 1H), 2.91(m, 1H), 2.71-2.58(m, 2H), 2.45(m, 1H), 2.09(m, 1H), 1.98(m, 2H), 1.68(m, 3H), 1.54(m, 1H)

25 MS : 405(M+1)⁺, 271, 202, 135

Example 7 : Synthesis of methyl 3-[[[(S)-2-[2-(6-amidino-1-methyl-indol-2-yl)ethyl]pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carboxylate (Compound 7)

30

a) Synthesis of methyl 3-[[[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]-pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carboxylate:

35 80mg of the compound I-b obtained in Example 2-b) was dissolved in dichloromethane and cooled to 0°C. To this solution, 59μl of triethyl-

amine was added and 110mg of methyl 3-bromomethylbenzo[b]thiophene-2-carboxylate was slowly added. The reaction mixture was stirred for 3.5 hours at room temperature and diluted with excess of dichloromethane. The organic layer was washed with water, dried over MgSO₄ and then filtered under reduced pressure. The filtrate was then concentrated. The concentrate was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(1:1)]. The fractions containing the desired product were combined and then evaporated to obtain 80mg of the title compound as a white solid.

10

b) Synthesis of methyl 3-[[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]-pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carboxylate:

80mg of the compound obtained in the above a) was dissolved in 5 ml of methanol and cooled to 0°C. HCl gas was bubbled into the solution for 50 minutes and the reaction solution was stirred at room temperature overnight and concentrated under reduced pressure to remove the solvent. The residue was dissolved in 5ml of methanol, and ammonia gas was bubbled for one hour at 0°C into the solution. The reaction solution was stirred at room temperature overnight and then distilled under reduced pressure. The residue was purified with column chromatography [eluent: dichloromethane/methanol(4:1)] on NH- DM1020 silica to obtain 22mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 8.13(d, 1H, J=8.06Hz), 7.88(s, 1H), 7.62(d, 1H, J=8.34Hz), 7.47-7.37(m, 3H), 6.30(s, 1H), 4.55(d, 1H, J=12.4Hz), 4.07(d, 1H, J=12.4Hz), 3.83(s, 3H), 3.67(s, 3H), 2.83-2.67(m, 4H), 2.26(m, 1H), 2.15-2.05(m, 2H), 1.69-1.57(m, 4H)

Example 8 : Synthesis of 3-[[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carboxamide (Compound 8)

1.46g of the compound I-a obtained in Example 1-1) was treated according to the same procedure as Example 7-a) to obtain 1.38g of the

white solid product, which was then treated according to the same procedure as Example 7-b) to obtain 930mg of the title compound as a pale yellow solid.

- 5 ¹H NMR(MeOH-d₄, ppm) : δ 7.95(d, 1H), 7.79(d, 1H), 7.73(m, 1H), 7.48(d, 1H), 7.33(m, 3H), 6.09(s, 1H), 4.22(d, 1H), 3.99(m, 2H), 3.92(d, 1H), 2.85(m, 1H), 2.68-2.61(m, 4H), 2.39(m, 1H), 2.15(m, 1H), 1.95(m, 1H), 1.74-1.58(m, 4H), 1.86(t, 3H)

10 Example 9 : Synthesis of 3-[[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carboxamide (Compound 9)

- 15 80mg of 3-[[[(S)-[2-(6-cyano-1-methylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]benzo[b]thiophene-2-carboxamide was treated according to the same procedure as Example 7-b) to obtain 36mg of the title compound as a pale yellow solid.

- 20 ¹H NMR(MeOH-d₄, ppm) : δ 7.90(d, 1H, J=7.5Hz), 7.77(d, 1H, J=7.42Hz), 7.71(s, 1H), 7.47(d, 1H, J=8.36Hz), 7.33-7.24(m, 3H), 6.10(s, 1H), 4.19(d, 1H, J=12.99Hz), 4.14(d, 1H, J=7.58Hz), 3.49(s, 1H), 2.85(m, 1H), 2.71-2.60(m, 3H), 2.40(m, 1H), 1.92(m, 1H), 1.73-1.58(m, 4H)

25 Example 10 : Synthesis of 1-methyl-2-[2-[(S)-1-[[2-(N-methyl-carbamoyl)benzo[b]thiophen-3-yl]methyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 10)

- 30 a) Synthesis of N-methyl [3-[[[(S)-2-[2-(6-cyano-1-methylindol-2-yl)-ethyl]pyrrolidinyl]methyl]benzo[b]thiophen-2-yl]formamide:

- 35 Methyl 3-[[[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]pyrrolidinyl]methyl]benzo[b]thiophene-2-carboxylate was dissolved in methanol solution of 40% methylamine and then stirred for 2 hours at room temperature. The reaction solution was evaporated to obtain the residue which was then purified with silica gel column chromatography [eluent:

dichloromethane/ethyl acetate(2:1)] to obtain 70mg of the title compound as a white foam.

¹H NMR(CDCl₃, ppm) : δ 10.64(d, 1H, J=4.83Hz), 7.88(d, 1H), 7.80(d, 1H), 7.55(d, 2H, J=8.19Hz), 7.40(m, 1H), 7.35-7.31(m, 2H), 6.22(s, 1H), 4.18(d, 1H), 3.87(d, 1H), 3.50(s, 3H), 3.02(d, 3H), 2.99(m, 1H), 2.77-2.70(m, 3H), 2.45(m, 1H), 2.13(m, 1H), 2.07(m, 1H), 1.85-1.82(m, 2H), 1.68-1.63(m, 2H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-[[2-(N-methylcarbamoyl)benzo[b]-thiophen-3-yl]methyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

35mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 25mg of the title compound.

¹H NMR(CDCl₃, ppm) : δ 10.67(d, 1H, J=4.17Hz), 8.08(s, 1H), 7.81-7.76(m, 2H), 7.49-7.45(m, 2H), 7.37-7.32(m, 2H), 6.10(s, 1H), 4.04(d, 1H), 3.57(s, 3H), 2.93(d, 3H), 2.86(brs, 1H), 2.65(m, 3H), 2.33(m, 1H), 2.20-2.17(m, 1H), 2.02-1.96(m, 1H), 1.77-1.73(m, 2H), 1.58-1.54(m, 2H)

Example 11 : Synthesis of 1-methyl-2-[2-[(S)-1-[(4-methoxyphenyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 11)

a) Synthesis of 1-methyl-2-[2-[(S)-1-[(4-methoxyphenyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

70mg of the compound I-b obtained in Example 2-b) and 67mg of p-methoxybenzoic acid were dissolved in dichloromethane, and 119mg of WSCIHCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) was added thereto. The reaction mixture was stirred for 2.5 hours at room temperature, and water was added thereto. The reaction solution was extracted two times with dichloromethane. The extracts were

combined, dried over MgSO_4 and then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(50:1)] to obtain 78mg of the title compound as a white solid.

- 5 ^1H NMR(CDCl_3 , ppm) : δ 7.54-7.45(m, 2H), 7.26(d, 1H), 7.20-7.13(dd, 2H), 6.90-6.80(dd, 2H), 6.39(s, 1H), 4.29-4.18(brs, 1H), 3.78(s, 3H), 3.66(s, 3H), 3.50(t, 2H), 2.79(t, 2H), 2.20-2.33(m, 1H), 1.97(m, 3H), 1.74(m, 2H)

- 10 b) Synthesis of 1-methyl-2-[2-[(S)-1-[(4-methoxyphenyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

78mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 26mg of the
15 title compound as a yellowish white solid.

- ^1H NMR($\text{MeOH}-d_4$, ppm) : δ 7.76(s, 1H), 7.48(d, 1H), 7.06(d, 2H), 6.77(d, 2H), 6.33(s, 1H), 4.13-4.05(brs, 1H), 3.65(s, 3H), 3.49(s, 3H), 3.54-3.40(m, 2H), 2.82-2.75(m, 2H), 2.25-1.60(m, 6H)

20

Example 12 : Synthesis of 1-methyl-2-[2-[(S)-1-[(3,4-dimethoxyphenyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 12)

- 25 a) Synthesis of 1-methyl-2-[2-[(S)-1-[(3,4-dimethoxyphenyl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

50mg of the compound I-b obtained in Example 2-b) and 52mg of 3,4-dimethoxybenzoic acid were reacted according to the same procedure
30 as Example 11-a) to obtain 53mg of the title compound as a white solid.

- ^1H NMR($\text{MeOH}-d_4$, ppm) : δ 7.77(s, 1H), 7.54(d, 1H), 7.25(d, 1H), 7.10(s, 2H), 7.00(d, 1H), 6.50(s, 1H), 4.38-4.25(brs, 1H), 3.83(s, 3H), 3.78(s, 3H), 3.65-3.50(m, 2H), 2.97-2.87(m, 2H), 2.28-1.60(m, 6H)

35

b) Synthesis of 1-methyl-2-[2-[(2S)-1-[(3,4-dimethoxyphenyl)carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

42mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 21mg of the title compound as a yellowish green solid.

¹H NMR(CDCl₃, ppm) : δ 7.47-7.40(d, 1H), 7.32-7.20(m, 1H), 7.09(brs, 2H), 6.83-6.81(br, 1H), 6.34(s, 1H), 4.33(brs, 1H), 3.89(s, 3H), 3.86(s, 3H), 3.73(bs, 2H), 3.48(s, 3H), 2.79(brs, 2H), 2.22-1.60(m, 6H)

Example 13 : Synthesis of 1-methyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 13)

500mg of the compound I-b obtained in Example 2-b) was dissolved in 10ml of dichloromethane, and 460μl of triethylamine and 0.35 ml of phenylacetyl chloride were added thereto. The reaction mixture was treated according to the same procedure as Example 1-m) to obtain 430mg of 1-methyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]-indole-6-carbonitrile, which was then treated according to the same procedure as Example 1-n) to obtain 267mg of the title compound.

¹H NMR(MeOH-d₄, ppm) : δ 7.92(m, 1H), 7.66(m, 1H), 7.61(m, 1H), 7.36-7.28(m, 5H), 6.46(s, 1H), 4.21(m, 1H), 3.85(s, 3H), 3.77(m, 2H), 3.60(t, 3H, J=6.60Hz), 2.84(m, 2H), 2.27(m, 1H), 1.99-1.82(m, 6H)

Example 14 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 14)

a) Synthesis of 1-ethyl-2-[2-[(2S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

80mg of the compound I-a obtained in Example 1-l) was dissolved

in dichloromethane and then cooled to 0°C. To this solution, 56 μ l of triethylamine was added and 53 μ l of phenylacetyl chloride was then slowly added. The reaction mixture was stirred for 4 hours at room temperature and then diluted with excess of dichloromethane. The organic layer was washed with water, dried over MgSO₄ and filtered under reduced pressure. The filtrate was concentrated. The concentrate was then purified with silica gel column chromatography [eluent: dichloromethane/methanol(10:1)]. The fractions containing the desired product were combined and evaporated to obtain 81mg of the title compound as a pale yellow solid.

b) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]-indole-6-carboxamide:

80mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 60mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.81(d, 1H, J=7.15Hz), 7.53(d, 1H, J=8.33 Hz), 7.30(d, 1H, J=8.33Hz), 7.22-7.13(m, 4H), 6.36(s, 1H), 4.14 (m, 3H), 3.62(d, 1H), 3.49(m, 2H), 2.73(t, 2H, J=8.13Hz), 2.15(m, 1H), 1.93-1.86(m, 5H), 1.26(t, 3H, J=7.15Hz)

Example 15 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-(3-chlorophenyl)-acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 15)

70mg of the compound I-a obtained in Example 1-l) and 67mg of 3-chlorophenylacetic acid were treated according to the same procedure as Example 11-a) to obtain 40mg of the pale yellow oily product. 38mg of this product was then treated according to the same procedure as Example 1-n) to obtain 18mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.84(s, 1H), 7.41(d, 1H, J=8.24Hz), 7.16-7.12(m, 4H), 7.06(m, 1H), 6.27(s, 1H), 4.15-4.10(m, 3H), 3.54(s, 2H), 3.49-3.42(m, 2H), 2.70-2.65(m, 2H), 2.24-2.20(m, 1H), 1.97-1.89

(m, 3H), 1.71-1.63(m, 2H), 1.25(t, 3H, J=7.00Hz)

Example 16 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-(3-hydroxyphenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 16)

a) Synthesis of 2-[3-(1,1,2,2-tetramethyl-1-silapropoxy)phenyl]acetic acid:

1g of 3-hydroxyphenylacetic acid was dissolved in 10ml of N,N-dimethylformamide, and 3.97g of TBDMSCl (ter-butyl dimethylsilyl chloride) and 2.69g of imidazole were added thereto. The reaction mixture was stirred for 14 hours at room temperature and then for 4 hours at 35°C. The reaction solution was diluted with 150ml of dichloromethane and then washed with saturated saline and 0.7N cold HCl solution. The organic layer was washed again with saturated saline, dried over sodium sulfate and filtered. The filtrate was concentrated. The residue was then dissolved in 20ml of methanol and 8ml of tetrahydrofuran, and aqueous K₂CO₃ solution (400mg/8ml) was added thereto. The reaction mixture was stirred for 1.5 hours at room temperature and then concentrated. To the residue was added saturated saline and the reaction solution was acidified with 10% aqueous citric acid solution to pH 4 and extracted with dichloromethane (100ml×2). The organic layer was washed with saturated saline, dried over sodium sulfate and then filtered. The filtrate was concentrated. The residue was then purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(1:1)] to obtain 1.69g of the title compound as a pale yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.02-6.95(m, 1H), 6.73-6.69(m, 1H), 6.59-6.53(m, 2H), 3.40(s, 2H), 0.79(s, 9H), 0.01(s, 6H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[3-(1,1,2,2-tetramethyl-1-silapropoxy)phenyl]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

300mg of the compound obtained in the above a) was treated

according to the same procedure as Example 11-a) to obtain 170mg of the title compound as a colorless oil.

¹H NMR(CDCl₃, ppm) : δ 7.42-7.36(m, 2H), 7.12-7.09(m, 1H), 7.02-6.97(m, 1H), 6.71-6.68(m, 1H), 6.61-6.54(m, 2H), 6.23(s, 1H), 4.13
5 (brs, 1H), 3.95(q, 2H), 3.45(s, 2H), 3.31-3.27(m, 2H), 2.60(t, 2H), 2.20-2.11(m, 1H), 1.81-1.74(m, 3H), 1.57-1.55(m, 2H), 1.18(t, 3H), J=7.20Hz), 0.78(s, 9H), 0.01(s, 6H)

10 c) Synthesis of 1-ethyl-2-[2-[(S)-1-[2-(3-hydroxyphenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

170mg of the compound obtained in the above b) was dissolved in 10ml of tetrahydrofuran and then cooled to 0°C. To the resulting
15 solution was added 1.65ml of 1.0M tetrabutylammonium fluoride solution, and the mixture was stirred for 45 minutes at the same temperature. After adding saturated saline, the reaction solution was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated. The residue was purified with
20 silica gel column chromatography [eluent: dichloromethane/ethyl acetate (1:1)] to obtain 120mg of the title compound as a colorless oil.

¹H NMR(CDCl₃, ppm) : δ 8.66(brs, 1H), 7.35-7.29(m, 2H), 7.12-7.07(m, 1H), 7.00-6.93(m, 2H), 6.60-6.50(m, 2H), 6.13(s, 1H), 4.13(brs, 1H), 3.87(m, 2H), 3.39(s, 2H), 3.31(m, 2H), 2.57-2.54(m, 2H),
25 2.12-2.09(m, 1H), 1.77-1.74(m, 3H), 1.58-1.43(m, 2H), 1.09(t, 3H)

d) Synthesis of 1-ethyl-2-[2-[(S)-1-[2-(3-hydroxyphenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

30 70mg of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 55mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.80(d, 1H), 7.54(d, 1H), 7.33(dd, 1H, J=8.35Hz, J=1.75Hz), 7.01(t, 1H), 6.60(m, 3H), 6.38(s, 1H), 4.18-4.14(m, 3H),
35

3.54-3.47(m, 4H), 2.73(t, 2H), 2.17-2.11(m, 1H), 1.92-1.73(m, 5H),
1.27(t, 3H)

Example 17 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[3-(carbamoyl-methoxy)phenyl]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 18)

a) Synthesis of ethyl 2-[3-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidin-2-yl]-2-oxoethyl]phenoxy]acetate:

58mg(0.146 mmole) of 1-ethyl-2-[2-[(S)-1-[2-(3-hydroxyphenyl)-acetyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile obtained in Example 16-c) and 26 μ l of ethyl bromoacetate were dissolved in 5ml of dimethylformamide and then cooled to 0°C. After adding NaH, the reaction mixture was stirred for 30 minutes at the same temperature and then for one hour at room temperature. 5ml of water was added, and the reaction solution was extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over sodium sulfate and then filtered. The filtrate was concentrated, and the residue was purified with silica gel column chromatography [eluent: dichloromethane/ethyl acetate(1:1)] to obtain 53mg of the title compound as a colorless oil.

¹H NMR(CDCl₃, ppm) : δ 7.42-7.37(m, 2H), 7.13-7.04(m, 2H), 6.76-6.70(m, 2H), 6.63(m, 1H), 6.24(s, 1H), 4.43(s, 2H), 4.12-4.04(m, 3H), 3.96(m, 2H), 3.46(s, 2H), 3.33(m, 2H), 2.60(t, 2H), 2.21-2.14(m, 1H), 1.82-1.77(m, 3H), 1.58-1.54(m, 2H), 1.19-1.09(m, 6H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[3-(carbamoylmethoxy)phenyl]-acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

38mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 18mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.81(d, 1H), 7.54(d, 1H), 7.32(m, 1H), 7.16(t,

1H), 6.83-6.78(m, 3H), 6.38(s, 1H), 4.37(s, 2H), 4.21-4.13(m, 3H), 3.60(d, 2H), 3.52-3.48(m, 2H), 2.74(t, 2H), 2.18-2.13(m, 1H), 1.97-1.86(m, 3H), 1.79-1.75(m, 2H), 1.26(t, 3H)

5 Example 18 : Synthesis of 2-[3-[2-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidin-2-yl]-2-oxoethyl]phenoxy]acetic acid (Compound 19)

7mg of 1-ethyl-2-[2-(S)-1-[2-[3-(carbamoylmethoxy)phenyl]acetyl]-pyrrolidin-2-yl]ethylindole-6-carboxamide obtained in Example 17
10 was dissolved in 0.5ml of acetic acid and 1ml of 3N HCl solution, and the resulting solution was heated to refluxing temperature and stirred for 3 hours under refluxing. The reaction solution was concentrated to remove the solvent and the residue was then purified with column chromatography [eluent: ethyl acetate/methanol(1:1)] on NH-DM1020
15 silica to obtain 4mg of the title compound as a pale yellow solid.

¹H NMR(CDCI₃, ppm) : δ 7.78(s, 1H), 7.50(d, 1H, J=7.58Hz), 7.35-7.28(m, 1H), 7.12-7.06(m, 1H), 6.75-6.69(m, 3H), 6.33(s, 1H), 4.24(s, 2H),
20 4.15-4.06(m, 3H), 3.58-3.47(m, 4H), 2.69-2.65(m, 2H), 2.14-2.09(m, 1H), 1.94-1.88(m, 3H), 1.80-1.73(m, 2H), 1.22(t, 3H)

25 Example 19 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[3-(trifluoromethyl)phenyl]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 20)

100mg of the compound I-a obtained in Example 1-l) and 120mg of 3-(trifluoromethyl)phenylacetic acid were reacted according to the same procedure as Example 11-a) to obtain 80mg of the product, which was
30 then treated according to the same procedure as Example 1-n) to obtain 34mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.94(m, 1H), 7.65-7.45(m, 6H), 6.46(s, 1H), 4.28(m, 3H), 3.82(m, 1H), 3.64(m, 2H), 2.87(t, 2H), 2.30(m, 1H),
35 2.05(m, 4H), 1.91-1.82(m, 2H), 1.36(m, 3H)

Example 20 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-(2-nitrophenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 21)

270mg of the compound 1-a obtained in Example 1-l) and 250mg of 2-nitrophenylacetic acid were reacted according to the same procedure as Example 11-a) to obtain 180mg of the white solid product. 60mg of the resulting product was then treated according to the same procedure as Example 1-n) to obtain 30mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 8.00(d, 1H), 7.76(m, 1H), 7.54-7.33(m, 5H), 6.31(s, 1H), 4.14(m, 3H), 3.96(m, 2H), 3.61(m, 2H), 2.72(t, 2H), 1.98-1.90(m, 6H), 1.80(m, 2H), 1.26(t, 3H)

Example 21 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[2-(methanesulfonylamino)phenyl]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 22)

110mg of 1-ethyl-2-[2-[(S)-1-[2-(2-nitrophenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile was dissolved in 10ml of ethanol, and 15mg of 10% Pd/C was added thereto. The reaction mixture was stirred for 4 hours in hydrogen atmosphere at room temperature under normal pressure and then filtered under reduced pressure. The filtrate was distilled under reduced pressure and dried to obtain 110mg of the product. To 70mg of the resulting product thus obtained was added 3ml of pyridine and methanesulfonyl chloride was then slowly added thereto at 0°C. The reaction mixture was stirred for 3 hours at 0°C, and excess of ethyl acetate was added thereto. The organic layer was washed three times with water and 1N aqueous HCl solution, dried over sodium sulfate and then filtered under reduced pressure. The filtrate was distilled under reduced pressure. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(1:2)]. The fractions containing the desired product were combined and distilled under reduced pressure to obtain 80mg of the white foamy product. 74mg of the product thereby obtained was treated according to the same procedure as Example

1-n) to obtain 34mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.81(m, 1H), 7.53(d, 1H), 7.29(m, 2H), 7.16
5 (m, 2H), 7.03(t, 1H), 6.37(s, 1H), 4.19-4.12(m, 3H), 3.75(d, 1H),
3.59(m, 2H), 2.84(s, 3H), 2.74(t, 2H, J=8.09Hz), 1.96-1.91(m, 4H),
1.77(m, 2H), 1.25(t, 3H)

10 Example 22 : Synthesis of ethyl 2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]-2-oxoethyl]benzoate
(Compound 23)

a) Synthesis of 2-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]-2-oxoethyl]benzoic acid:

15 985mg of the compound I-a obtained in Example 1-1) was dissolved in 40ml of ethanol, and 956mg of 75% homophthalic anhydride and 1.05ml of triethylamine were added thereto. The resulting solution was stirred for one hour at room temperature and distilled under reduced pressure to remove ethanol. To the residue was added water. The
20 mixture was extracted with dichloromethane. The organic layer was then washed with 1N-HCl and water, dried over sodium sulfate, and then filtered. The filtrate was distilled under reduced pressure to obtain 1.57g of the title compound as a yellow foamy solid.

25 ¹H NMR(CDCl₃, ppm) : δ 7.95(dd, 1H, J=7.80Hz, 1.30Hz), 7.50-7.44(m, 2H), 7.37-7.34(m, 2H), 7.17-7.25(m, 2H), 6.33(s, 1H), 4.28(s, 2H), 4.06-3.98(m, 3H), 3.94-3.91(m, 2H), 3.75-3.71(m, 2H), 2.24-2.21 (m, 1H), 2.10-2.05(m, 3H), 1.79-1.72(m, 2H), 1.25-1.21(m, 3H)

30 b) Synthesis of ethyl 2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]-2-oxoethyl]benzoate:

150mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 50mg of the
35 title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.87(dd, 1H, J=7.85Hz, 1.40Hz), 7.76(s, 1H),
7.48(d, 1H, J=8.30Hz), 7.39(d, 1H, J=1.50Hz), 7.30-7.25(m, 2H),
7.18-7.15(m, 1H), 6.32(s, 1H), 4.14-4.09(m, 5H), 3.93(d, 2H,
J=7.96Hz), 3.58-3.55(m, 2H), 2.74-2.71(m, 2H), 2.14-2.11(m, 1H),
1.96-1.93(m, 3H), 1.83-1.80(m, 2H), 1.19-1.11(m, 6H)

ES-MS : 475(M+1)⁺

**Example 23 : Synthesis of 2-[2-[(S)-2-[2-(6-amidino-1-ethylin-
dol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]benzoic acid (Compound 24)**

150mg of 2-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrro-
lidinyl]-2-oxoethyl]benzoic acid obtained in Example 22-a) was treated
according to the same procedure as Example 1-n) to obtain 28mg of the
title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.68(s, 1H, J=7.60Hz), 7.62(dd, 1H, J=7.60
Hz, 2.00Hz), 7.43(d, 1H, J=8.30Hz), 7.22-7.15(m, 4H), 6.37(s, 1H),
4.15-4.10(m, 4H), 3.85(d, 1H, J=15.80Hz), 3.54-3.51(m, 2H),
2.77-2.74(m, 2H), 2.21-2.16(m, 1H), 1.98-1.93(m, 3H), 1.82-1.78
(m, 2H), 1.28-1.22(m, 3H)

ES-MS : 447(M+1)⁺

**Example 24 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-2-
phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide
(Compound 30)**

a) Synthesis of 2-cyclopentyl-2-phenylacetyl chloride:

In a 100ml flask, 0.2g of 2-cyclopentyl-2-phenylacetic acid was
introduced and 8ml of thionyl chloride was slowly added thereto at 0°C.
The reaction mixture was stirred for 4 hours at 70°C and then evaporated
under reduced pressure to remove the solvent. The residue was dried
under reduced pressure to obtain 0.2g of the title compound as a brown
oil.

b) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-2-phenylacetyl)pyrro-

lidin-2-yl]ethyl]indole-6-carbonitrile:

300mg of the compound I-a obtained in Example 1-l) and 30mg of 2-cyclopentyl-2-phenylacetyl chloride were treated according to the same procedure as Example 1-m) to obtain 30mg of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.53(m, 2H), 7.36-7.21(m, 6H), 6.28(s, 1H), 4.33(m, 1H), 4.13(m, 2H), 3.59(m, 1H), 3.38-3.30(m, 2H), 2.64(m, 3H), 2.07-1.92(m, 6H), 1.62(m, 6H), 1.26(m, 3H), 1.09(m, 2H)

c) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

26mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 20mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 8.03(s, 1H), 7.40-7.18(m, 7H), 6.16(s, 1H), 4.27(m, 1H), 4.10 (m, 2H), 3.55(m, 1H), 3.37-3.28(m, 2H), 2.58(m, 3H), 2.01-1.90(m, 6H), 1.57(m, 6H), 1.25(m, 3H), 1.07(m, 2H)

Example 25 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-hydroxy-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 31)

250mg of the compound I-a obtained in Example 1-l) and 140mg of benzoylformic acid were dissolved in 10ml of dichloromethane, and 358mg of WSCIHCl was then slowly added thereto at 0°C. The reaction mixture was stirred at room temperature overnight, and excess of dichloromethane was added thereto. The organic layer was washed with water, dried over anhydrous magnesium sulfate and then filtered under reduced pressure. The filtrate was distilled under reduced pressure. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(2:1)]. The fractions containing the desired

product were combined and distilled under reduced pressure to obtain 83 mg of the product, which was then dissolved in 5ml of methanol, and 16mg of NaBH₄ was added at room temperature thereto. The mixture was stirred for one hour and then distilled under reduced pressure to remove the reaction solvent. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(1:1)]. The fractions containing the desired product were combined and then distilled under reduced pressure to obtain 15mg of the white solid product, which was then treated according to the same procedure as Example 1-n) to obtain 7 mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.81(m, 1H), 7.55(d, 1H), 7.34-7.23(m, 6H), 6.41(s, 1H), 4.23(m, 2H), 4.10(m, 1H), 3.49(m, 2H), 3.10(m, 1H), 2.78(t, 2H), 2.25(m, 1H), 1.91(m, 1H), 1.79-1.72(m, 5H), 1.30(t, 3H)

Example 26 : Synthesis of 1-methyl-2-[2-[(S)-1-[(R)-2-acetyl-amino-2-(4-hydroxyphenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 32)

1.00g of the compound I-b obtained in Example 2-b) and 1.11g of (R)-2-(acetyl-amino)-2-(4-acetyloxyphenyl)acetic acid were treated according to the same procedure as Example 11-a) to obtain 1.67g of 4-[2-[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]pyrrolidinyl]-(R)-1-acetyl-amino-2-oxoethyl]phenyl acetate. 96mg of the compound thereby obtained was treated according to the same procedure as Example 1-n) to obtain 48mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.80(s, 1H), 7.52(d, 1H, J=8.25Hz), 7.32(d, 1H, J=8.33Hz), 7.08(d, 2H, J=8.46Hz), 6.62(d, 2H, J=9.42Hz), 6.36(s, 1H), 4.09(brs, 1H), 3.70(s, 3H), 1.86(s, 3H)

Example 27 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-2-methyl-sulfonylamino-2-phenylacetyl]pyrrolidin-2-yl]ethyl]indole-6-carbox-amidine (Compound 37)

1.00g of (R)-(-)-2-phenylglycine, 10ml of 1,4-dioxane and 10ml of 2N aqueous NaOH solution were mixed, and 1.73g of (BOC)₂O was slowly added at 0°C. The reaction mixture was stirred overnight at room temperature and distilled under reduced pressure to remove 1,4-dioxane. To the residue were added 50ml of water and 5ml of aqueous NH₄OH solution. The aqueous layer was washed with dichloromethane, acidified with c-HCl, and then extracted with ethyl acetate. The extract was dried over sodium sulfate and distilled under reduced pressure to obtain 1.6g of liquid (R)-2-[(tert-butoxy)carbonyl-amino]-2-phenylacetic acid. 507mg of (R)-2-[(tert-butoxy)carbonyl-amino]-2-phenylacetic acid and 450mg of 1-ethyl-2-[(S)-pyrrolidin-2-yl]ethylindole-6-carbonitrile were then treated according to the same procedure as Example 11-a) to obtain the product, which was then dissolved in dichloromethane. To the resulting solution, 4ml of trifluoroacetic acid was added. The reaction solution was stirred overnight at room temperature and extracted with excess of dichloromethane. The organic layer was neutralized with aqueous NaHCO₃ solution and then extracted with dichloromethane. The extract was dried over MgSO₄ and filtered under reduced pressure. The filtrate was then distilled under reduced pressure. The remaining residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(10:1)]. The fractions containing the desired product were combined and then distilled under reduced pressure to obtain 290mg of the white solid product. 80mg of the resulting product 1-ethyl-2-[2-[(S)-1-((R)-2-amino-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile was dissolved in 5ml of dichloromethane, and triethylamine (0.299 mmole) and methanesulfonyl chloride (0.299 mmole) were added at 0°C thereto. The reaction mixture was stirred for 3 hours at 0°C and excess of dichloromethane was added thereto. The organic layer was washed with water, dried over Na₂SO₄ and then filtered under reduced pressure. The filtrate was evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent : n-hexane/ethyl acetate(1:2)] to obtain 90mg of the white foamy solid product. Finally, 70mg of the resulting compound, 1-ethyl-2-[2-[(S)-1-((R)-2-methylsulfo-

nylamino-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile was treated according to the same procedure as Example 1-n) to obtain 28mg of the title compound as a pale yellow solid.

5 ¹H NMR(MeOH-d₄, ppm) : δ 7.81(s, 1H), 7.55(d, 1H, J=8.08Hz), 7.37-7.19(m, 6H), 6.39(s, 1H), 5.21(s, 1H), 4.23-4.12(m, 3H), 3.62(m, 1H), 3.12(m, 1H), 2.80(t, 2H), 2.68(s, 3H), 2.25(m, 1H), 1.93(m, 2H), 1.81-1.74(m, 6H), 1.30(t, 3H)

10 Example 28 : Synthesis of ethyl 2-[[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenyl]ethyl]-aminolacetate (Compound 38)

15 192mg of 1-ethyl-2-[2-[(S)-1-((R)-2-amino-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile obtained in Example 27 and 120mg of ethyl bromoacetate were treated according to the same procedure as Example 1-m) to obtain 129mg of ethyl 2-[[[(R)-2-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenylethyl]amino]acetate. 120mg of the resulting compound was treated according to the same
20 procedure as Example 1-n) to obtain 34mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.81(s, 1H), 7.54(t, 1H), 7.48-7.22(m, 6H), 6.39(s, 1H), 4.52(s, 1H), 4.21(m, 2H), 4.06-4.01(m, 2H), 3.56(m, 25 2H), 3.05(m, 1H), 2.78(m, 2H), 2.25(m, 1H), 1.80-1.68(m, 7H), 1.29(t, 3H, J=7.10Hz), 1.13(m, 3H)

Example 29 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-2-(carbamoylmethylamino)-2-phenylacetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 39)
30

129mg of ethyl 2-[[[(R)-2-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenyl]ethyl]amino]acetate obtained in Example 28 was treated according to the same procedure as Example
35 1-n) to obtain 40mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.81(s, 1H), 7.50(m, 1H), 7.34-7.13(m, 6H), 6.39(s, 1H), 4.46(s, 1H), 4.21(d, 2H), 4.08(m, 1H), 3.60(m, 1H), 3.24-2.97(m, 3H), 2.77(t, 2H, J=7.58Hz), 2.30(m, 1H), 1.92(m, 2H), 1.80-1.68(m, 5H), 1.28(t, 3H, J=6.93Hz)

5

Example 30 : Synthesis of 2-[[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenylethyl]amino]acetic acid (Compound 40)

10 To 20mg of ethyl 2-[[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenyl]ethyl]amino]acetate obtained in Example 28 was added concentrated HCl solution, and the reaction solution was stirred overnight while heating to 50-55°C and then distilled under reduced pressure to remove the solvent. The residue was purified
15 with column chromatography [eluent: methanol] on NH-DM1020 silica to obtain 14mg of the title compound as a white solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.77(s, 1H), 7.46(t, 1H, J=7.58Hz), 7.36-7.21(m, 6H), 6.33(s, 1H), 4.51(s, 1H), 4.20-4.08(m, 4H),
20 3.02(m, 2H), 2.76(t, 3H, J=7.90Hz), 2.25(m, 1H), 1.91(m, 2H), 1.77-1.68(m, 5H), 1.26(m, 3H)

20

Example 31 : Synthesis of 1-methyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 42)

25

a) Synthesis of 1-methyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

100mg of the compound I-b obtained in Example 2-b) and 0.055ml of cyclopentylacetic acid were reacted according to the same procedure as
30 Example 11-a) to obtain 32mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.57(m, 2H), 7.29(m, 1H), 6.40(s, 1H), 4.25(d, 1H),
35 3.71(s, 3H), 3.48(m, 2H), 2.80(t, 2H), 2.28(m, 4H), 1.98(m,

4H), 1.88 (m, 2H), 1.75(m, 2H), 1.59(m, 3H), 1.16(m, 2H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

5

32mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 20mg of the title compound as a pale yellow solid.

10 ¹H NMR(CDCl₃, ppm) : δ 7.95(s, 1H), 7.27(m, 2H), 7.13-6.84(br, 2H), 6.12 (s, 1H), 4.03(m, 1H), 3.56(s, 3H), 3.33(m, 2H), 2.55(m, 2H), 2.13 (m, 4H), 1.84-1.70(m, 6H), 1.52-1.40(m, 5H), 1.03(m, 2H)

ES-MS : 380(M+1)⁺

15 Example 32 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-acetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 43)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl]-ethyl]indole-6-carbonitrile:

20

100mg of the compound I-a obtained in Example 1-l) and 0.052ml of cyclopentylacetic acid were reacted according to the same procedure as Example 11-a) to obtain 30mg of the title compound as a pale yellow solid.

25

¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.29(m, 1H), 6.40(s, 1H), 4.28(m, 1H), 4.15(m, 2H), 3.50(m, 2H), 2.79(t, 2H), 2.30(m, 4H), 1.98(m, 3H), 1.87(m, 2H), 1.75(m, 2H), 1.59(m, 4H), 1.35(m, 3H), 1.18(m, 2H)

30

b) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl]-ethyl]indole-6-carboxamidine:

29mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 19mg of the

35

title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 8.06(m, 1H), 7.37(m, 2H), 6.91-6.52(br, 4H),
6.22(s, 1H), 4.17(m, 3H), 3.43(m, 2H), 2.67(m, 2H), 2.25(m, 4H),
1.94-1.71(m, 7H), 1.56(m, 4H), 1.21(m, 3H), 1.13(m, 2H)
ES-MS : 394(M+1)⁺

Example 33 : Synthesis of ethyl 3-[(S)-2-[2-(6-amidino-1-ethyl-
indol-2-yl)ethyl]pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate
(Compound 44)

a) Synthesis of ethyl 3-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-
pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate:

In a 100ml flask, 1g of the compound I-a) obtained in Example 1-l) and 1g of α-ethylcarboxylate cyclopentane acetyl chloride were introduced and reacted according to the same procedure as Example 1-n) to obtain 0.5g of the title compound as a pale brown oil.

¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.28(m, 1H), 6.40(m, 1H), 4.31(m, 1H), 4.17(m, 4H), 3.70(m, 1H), 3.59(m, 1H), 3.30(d, 1H), 2.81(m, 2H), 2.68(m, 1H), 2.28(m, 1H), 2.02(m, 5H), 1.77(m, 2H), 1.61(m, 5H), 1.35(m, 3H), 1.22(m, 3H), 1.09(m, 1H)

b) Synthesis of ethyl 3-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-
pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate:

0.4g of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 0.31g of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.98(m, 1H), 7.47(m, 1H), 7.33(m, 1H), 6.30(s, 1H), 4.16(m, 5H), 3.69-3.56(m, 2H), 3.30(d, 1H), 2.73(m, 3H), 2.25(m, 1H), 1.98(m, 5H), 1.72-1.58(m, 7H), 1.31-1.21(m, 6H), 1.03(m, 1H)

ES-MS : 466(M+1)⁺

Example 34 : Synthesis of 3-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-cyclopentyl-3-oxopropanoic acid (Compound 45)

In a 50ml flask, 80mg of ethyl 3-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate obtained in Example 33 was dissolved in 20ml of ethanol, and 10ml of 2N NaOH was added thereto. The reaction mixture was stirred for 10 hours at room temperature, neutralized with 10% aqueous citric acid solution, and then distilled under reduced pressure to remove the solvent. The residue was then purified with column chromatography [eluent: ethyl acetate/methanol (5:1)] on NH-DM1020 silica to obtain 51mg of the title compound as a yellowish white solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.87(s, 1H), 7.60(d, 1H), 7.38(d, 1H), 6.44(s, 1H), 4.28(m, 2H), 3.87(m, 1H), 3.65(m, 1H), 3.19(d, 1H), 2.89(m, 3H), 2.59(m, 1H), 2.24(m, 1H), 2.03(m, 5H), 1.84(m, 4H), 1.59(m, 4H), 1.32(m, 3H)

IR(KBr) : 3420, 2890, 1620 cm⁻¹

ES-MS : 439(M+1)⁺, 462(M+Na)

Example 35 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclohexylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 46)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclohexylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

100mg of the compound I-a obtained in Example 1-1) and 88mg of cyclohexylacetic acid were reacted according to the same procedure as Example 11-a) to obtain 60mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.30(m, 1H), 6.40(s, 1H), 4.28(m,

1H), 4.15(m, 2H), 3.47(t, 2H), 2.79(t, 2H), 2.28(m, 1H), 2.17(m, 1H), 1.99(m, 4H), 1.74-1.67(m, 7H), 1.38(m, 4H), 1.26(m, 3H), 0.94(m, 2H)

- 5 b) Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclohexylacetyl)pyrrolidin-2-yl]-ethyl]indole-6-carboxamide:

50mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 40mg of the
10 title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 8.02(s, 1H), 7.73-7.54(br, 2H), 7.43(m, 2H), 6.25(s, 1H), 4.13(m, 3H), 3.48(m, 2H), 2.68(m, 2H), 2.21(m, 1H), 2.13(m, 1H), 1.92(m, 4H), 1.69-1.63(m, 7H), 1.27(m, 7H), 0.93(m, 2H)
15

ES-MS : 409(M+1)⁺

20 Example 36 : Synthesis of 1-ethyl-2-[2-[(S)-[1-(3-phenylpropanoyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 50)]

60mg of the compound I-a obtained in Example 1-l) and 40mg of 3-phenylpropanoic acid were reacted according to the same procedure as Example 11-a) to obtain 55mg of the product, which was then treated according to the same procedure as Example 1-n) to obtain 40mg of the
25 title compound.

¹H NMR(CDCl₃, ppm) : δ 8.08(m, 1H), 7.61(m, 1H), 7.44(m, 1H), 7.34-7.17(m, 5H), 6.28(s, 1H), 4.19(m, 3H), 3.36-2.95(m, 2H), 2.92(t, 2H), 2.86(m, 4H), 2.69(m, 2H), 2.54(t, 2H), 2.27(m, 1H), 1.73-1.63(m, 2H)
30

35 Example 37 : Synthesis of 1-methyl-2-[2-[(S)-1-[(R)-2-acetyl-amino-3-phenylpropanoyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 53)]

1.00g of the compound I-b obtained in Example 2-b) and 1.00g of (2)-2-acetylamino-3-phenylpropanoic acid were treated according to the same procedure as Example 11-a) to obtain 1.37g of N-[(R)-2-[(S)-2-[2-(6-cyano-1-methylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-benzylethyl]-ethanamide. 78mg of the compound thereby obtained was treated according to the same procedure as Example 1-n) to obtain 32mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.79(s, 1H), 7.48(d, 1H), 7.18(d, 1H), 7.14(m, 5H), 6.31(s, 1H), 4.20-3.90(brs, 1H), 3.66(s, 3H), 2.84(s, 3H)

Example 38 : Synthesis of 1-ethyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 57)

150mg of the compound I-b obtained in Example 2-b) was reacted with 96mg of chloroacetyl chloride under the same conditions as Example 1-m) to obtain the product, which was then dissolved in N,N-dimethylformamide. To the resulting solution were added 50mg of cyclopropylamine and K₂CO₃. The reaction mixture was stirred overnight at room temperature and extracted with ethyl acetate. The extract was dried over MgSO₄ and then filtered. The filtrate was concentrated under reduced pressure to obtain the residue, which was then purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane (4:1)] to obtain 120mg of the pale yellow solid product, 1-ethyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile. The product thereby obtained was treated according to the same procedure as Example 1-n) to obtain 45mg of the title compound as a pale yellow solid.

ES-MS : 382(M+1)⁺

Example 39 : Synthesis of 1-ethyl-2-[2-[(S)-1-[2-[cyclopropyl(methylsulfonyl)amino]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 58)

100mg of
1-ethyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole
-6-carbonitrile obtained in Example 38 was reacted with 60mg of
methanesulfonyl chloride in 2ml of pyridine to obtain 90mg of the product,
5 which was then treated according to the same procedure as Example 1-n)
to obtain 55mg of the title compound as a pale yellow solid.

ES-MS : 460(M+1)⁺

10 Example 40 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-
methylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopropylamino]-
acetate (Compound 59)

300mg of the compound I-b obtained in Example 2-b) was reacted
15 according to the same procedure as Example 38 to obtain 290mg of 1-
methyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole
-6-carbonitrile, which was then reacted with 170mg of ethyl 2-bromo-
acetate according to the same procedure as Example 1-m) to obtain 250mg
of the yellow solid product. The resulting product was then treated
20 according to the same procedure as Example 1-n) to obtain 85mg of the
title compound as a pale yellow solid.

¹H-NMR(MeOH-d₄, ppm) : δ 7.80(d, 1H, J=3.28Hz), 7.56-7.51(m, 1H),
7.32(d, 1H, J=8.32Hz), 6.36(s, 1H), 4.08-3.93(m, 5H), 3.71(s, 3H),
25 3.37-3.34(m, 4H), 2.74-2.61(m, 3H), 2.18-2.11(m, 1H), 1.92(m,
1H), 1.80-1.77(m, 2H), 0.82-0.78(m, 3H), 0.58-0.65(m, 3H), 0.36
(m, 1H)

30 Example 41 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-
methylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopentylamino]-
acetate (Compound 60)

100mg of 1-methyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrro-
lidin-2-yl]ethyl]indole-6-carbonitrile obtained in Example 40 and 60mg of
35 cyclopentylamine were reacted according to the same procedure as

Example 38 to obtain 95mg of the yellow solid product, which was then reacted with ethyl 2-bromoacetate according to the same procedure as Example 1-m) to obtain 70mg of the pale yellow solid product. The resulting product was then treated according to the same procedure as
5 Example 38 to obtain 48mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.80(s, 1H), 7.54-7.51(m, 1H), 7.35-7.31(m, 1H), 6.37(s, 1H), 4.58(m, 2H), 4.38-4.31(m, 1H), 4.08-4.02(m, 2H), 3.91(m, 2H), 3.71(s, 3H), 3.65-3.61(m, 1H), 3.45-3.40(m, 2H), 2.79-2.73(m, 2H), 2.13-2.08(m, 1H), 1.93(m, 3H), 1.80-1.77(m, 4H), 1.57(br, 2H), 1.41(br, 4H), 0.82-0.78(m, 3H)
10

Example 42 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]benzylaminol]acetate
15 (Compound 61)

150mg of the compound I-b obtained in Example 2-b) was treated according to the same procedure as Example 1-m) to obtain the product, to which 70mg of ethyl 2-(benzylamino)acetate, 101mg of K₂CO₃ and 2.5ml of dimethylformamide were added. The resulting mixture was stirred overnight at room temperature and extracted with ethyl acetate. The extract was dried over MgSO₄ and filtered. The filtrate was then concentrated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(4:1)] to
20 obtain 120mg of the pale yellow solid product, which was treated according to the same procedure as Example 1-n) to obtain 45mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.77-7.31(m, 4H), 7.28-7.19(m, 4H), 6.37(s, 1H), 4.89-4.45(m, 6H), 4.16-3.93(m, 3H), 3.69(d, 3H, J=8.84Hz), 3.44-3.37(m, 2H), 2.81-2.75(m, 2H), 2.18-1.71(m, 6H), 0.82-0.77(m, 3H)
30

ES-MS : 504(M+1)⁺

35 Example 43 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-

ethylindol-2-yl)ethylpyrrolidinyl]-2-oxoethylcyclopropylamino]acetate (Compound 62)

- 5 a) Synthesis of 1-ethyl-2-[2-((S)-1-2-chloroacetylpyrrolidin-2-yl)ethyl]-indole-6-carbonitrile:

300mg of the compound I-a obtained in Example 1-l) and 130mg of chloroacetyl chloride were reacted according to the same procedure as Example 1-m) to obtain 351mg of the title compound.

10

^1H NMR(CDCl_3 , ppm) : δ 7.65-7.55(m, 2H), 7.40-7.30(m, 1H), 6.45(s, 1H), 4.40-4.30(m, 1H), 4.25-4.20(q, 2H), 4.10(s, 2H), 3.70-3.55(m, 2H), 2.90-2.80(t, 2H), 2.40-2.30(m, 1H), 2.20-1.95(m, 4H), 1.90-1.75(m, 1H), 1.45-1.35(t, 3H)

15

- b) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-oxoethyl]cyclopropylamino]acetate:

351mg of the compound obtained in the above a) was dissolved in dimethylformamide, and 306mg of K_2CO_3 and 238mg of N-ethylacetato-cyclopropylamine were added. The reaction mixture was stirred overnight at room temperature and extracted with ethyl acetate. The extract was dried over MgSO_4 and filtered, and the filtrate was then concentrated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(4:1)] to obtain 373mg of the title compound as an oil.

25

^1H NMR(CDCl_3 , ppm) : δ 7.65-7.55(m, 2H), 7.30-7.20(m, 1H), 6.50-6.40(m, 1H), 4.35-4.10(m, 6H), 3.75-3.40(m, 6H), 2.90-2.80(m, 2H), 2.50-2.30(m, 1H), 2.20-1.95(m, 1H), 1.45-1.25(m, 1H), 0.95-0.70(m, 2H), 0.55-0.50(m, 2H)

30

- c) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-oxoethyl]cyclopropylamino]acetate:

35

55mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 24mg of the title compound.

¹H NMR(CDCl₃, ppm) : δ 7.70(m, 1H), 7.40(m, 1H), 7.20(m, 1H), 6.25(s, 1H), 4.55-4.40(d, 1H), 4.20-3.80(m, 5H), 3.50-3.10(m, 6H), 2.80-2.70(m, 2H), 2.20-1.65(m, 6H), 1.20-1.00(m, 6H), 0.75-0.65(m, 4H)

Example 44 : Synthesis of 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopropylaminolacetic acid (Compound 63)

40mg of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopropylamino]acetate obtained in Example 43 was dissolved in 50ml of ethanol, and 2ml of 2N NaOH was added thereto. The reaction mixture was stirred for 2 hours and then evaporated under reduced pressure to remove the solvent. The residue was purified with column chromatography [eluent: ethanol] on NH-DM 1020 silica to obtain 25mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.81-7.30(m, 3H), 6.37(s, 1H), 4.22-4.04(m, 3H), 3.56-3.43(m, 4H), 3.28(s, 2H), 2.81-2.67(m, 2H), 2.37(m, 1H), 2.23-1.70(m, 6H), 1.30-1.22(m, 3H), 0.64-0.25(m, 4H)

ES-MS : 440(M+1)⁺

Example 45 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclo-propylaminolacetate (Compound 64)

a) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate:

500mg of 1-ethyl-2-[2-((S)-1-2-bromopropanoylpyrrolidin-2-yl)-ethyl]indole-6-carbonitrile and cyclopropylamine were dissolved in dry

N,N-dimethylformamide, and 104mg of NaHCO₃ and 20.4mg of KI were added thereto. The reaction mixture was heated under refluxing for one hour and, after water was added, extracted with ethyl acetate. The extract was dried and distilled under reduced pressure. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain the title compound in a quantitative yield.

b) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate:

467mg of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate was dissolved in 15ml of acetonitrile, and diisopropylethylamine and ethyl-2-bromoacetate were added thereto. The reaction mixture was heated to 70°C and stirred for 4 hours. The reaction solution was concentrated under reduced pressure to obtain the residue, which was then purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 538mg of the title compound as a pale yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.79(s, 1H), 7.58(d, 1H, J=8.10Hz), 7.28(d, 1H, J=7.96Hz), 6.45(s, 1H), 4.35-3.90(m, 8H), 3.60-3.40(m, 3H), 2.84(m, 2H), 2.38-1.70(m, 8H), 1.42-1.13(m, 9H), 0.48(m, 3H),
ES-MS : 465(M+1)⁺

c) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate:

500mg of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 114mg of the title compound.

¹H NMR(MeOH-d₄, ppm) : δ 7.89(s, 1H), 7.61(d, 1H, J=8.29Hz), 7.42(d, 1H, J=8.22Hz), 6.44(s, 1H), 4.40-3.91(m, 6H), 3.70-3.40(m, 4H),

2.84(m, 2H), 2.40-1.70(m, 8H), 1.41(t, 3H), 1.23(m, 6H), 0.50(m, 3H)

ES-MS : 482(M+1)⁺

5 Example 46 : Synthesis of 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]-acetic acid (Compound 65)

32mg of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate was treated
10 according to the same procedure as Example 44 to obtain 27mg of the title compound as a yellowish white solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.82(s, 1H), 7.52(d, 1H), 7.32(d, 1H), 6.36(s,
15 1H), 4.30-3.80(m, 6H), 3.51-3.12(m, 3H), 2.73(m, 2H), 2.30-1.60
(m, 6H), 1.26(t, 3H), 1.13(m, 3H), 0.62-0.25(m, 4H)

ES-MS : 454(M+1)⁺

20 Example 47 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-(1R)-1-methyl-2-oxoethyl]aminol]-acetate (Compound 66)

a) Synthesis of N-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-(1R)-1-methyl-2-oxoethyl] (tert-butoxy)formamide:
25

406mg of the compound I-a obtained in Example 1-1) and 316mg of N-(tert-butoxy)carbonyl-D-alanine were reacted according to the same procedure as Example 11-a) to obtain 290mg of the title compound as a white solid.

30 ¹H-NMR(CDCl₃, ppm) : δ 7.61-7.54(m, 2H), 7.30(m, 1H), 6.42(s, 1H), 5.37
(d, 1H, J=8.44Hz), 4.47-4.39(m, 1H), 4.20-4.11(m, 3H), 3.74-3.40
(m, 2H), 2.79(t, 2H, J=7.91Hz), 2.39-1.77(m, 6H), 1.43(s, 9H),
35 1.37(t, 3H, J=7.23Hz), 1.25(d, 3H, J=7.13Hz)

b) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-(1R)-1-methyl-2-oxoethyl]amino]ethanoate:

274mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain the pale yellow solid product, which was then reacted with 0.076ml of ethyl 2-bromoacetate under the same conditions as Example 1-m) to obtain 187 mg of the title compound as a pale yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.62-7.55(m, 2H), 7.30(m, 1H), 6.43(s, 1H), 4.26 (brs, 1H), 4.21-4.13(m, 4H), 3.50, 3.64(m, 3H), 3.41(d, 1Ha, J=16.68Hz), 3.25(d, 1Hb, J=16.70Hz), 2.81(t, 2H, J=8.00Hz), 2.41-1.71(m, 6H), 1.37(t, 3H, J=7.21Hz), 1.27-1.23(m, 6H)

c) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-(1R)-1-methyl-2-oxoethyl]amino]acetate:

183mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 144mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.81(s, 1H), 7.60-7.32(m, 2H), 6.40(s, 1H), 4.22-4.01(m, 5H), 3.86-3.72(m, 1H), 3.59-3.27(m, 4H), 2.84-2.68 (m, 2H), 2.26-1.77(m, 6H), 1.30(t, 3H, J=7.13Hz), 1.15-1.06(m, 6H)

IR(KBr) cm⁻¹ : 3400, 2970, 1720, 1660, 1625, 1520, 1460

ES-MS : 442(M+1)⁺

Example 48 : Synthesis of 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-(1R)-1-methyl-2-oxoethyl]amino]acetic acid (Compound 67)

130mg of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-(R)-1-methyl-2-oxoethyl]amino]acetate was treated according to the same procedure as Example 44 to obtain 60mg of the title

compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.76(s, 1H), 7.57-7.27(m, 2H), 6.35(s, 1H),
4.21-4.06(m, 3H), 3.66-3.40(m, 3H), 3.01(s, 2H), 2.82-2.73(m,
5 2H), 2.27-1.71(m, 6H), 1.27(t, 3H, J=7.08Hz), 1.13-1.05(m, 3H)
ES-MS : 414(M+1)⁺

Example 49 : Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-
ethylindol-2-yl)ethyl]pyrrolidinyl]-(1R)-1-hydroxymethyl-2-oxo-
10 ethylaminolacetate (Compound 69)]

a) Synthesis of N-[2-[[[(S)-2-[2-(6-Cyano-1-ethylindol-2-yl)ethyl]pyrro-
lidinyl]-(R)-1-hydroxymethyl-2-oxoethyl]-(1,1-dimethylethyloxy)meth-
anamide:

15 412mg of the compound I-a obtained in Example 1-l) and 348mg of
N-(tert-butoxy)carbonyl-D-serine were reacted under the same conditions
as Example 11-a) to obtain 110mg of the title compound as a viscous oil.

20 ¹H NMR(CDCl₃, ppm) : δ 7.61-7.54(m, 2H), 7.30(m, 1H), 6.41(s, 1H), 5.55
(brs, 1H), 4.49(m, 1H), 4.28-4.13(m, 3H), 3.90-3.52(m, 4H),
3.22(brs, 1H), 2.82-2.75(m, 2H), 2.40-1.77(m, 6H), 1.44(s, 9H),
1.38(t, 3H, J=8.76Hz)

25 b) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-
pyrrolidinyl]-(1R)-1-hydroxymethyl-2-oxoethyl]amino]ethanoate:

109mg of the compound obtained in the above a) was treated
according to the same procedure as Example 1-l) to obtain the pale
30 yellow solid product, which was then reacted with 0.029ml of ethyl
2-bromoacetate under the same conditions as Example 1-m) to obtain 20
mg of the title compound as a pale yellow oil.

35 ¹H NMR(CDCl₃, ppm) : δ 7.62-7.55(m, 2H), 7.30(m, 1H), 6.41(s, 1H),
4.87-4.38(m, 2H), 4.31-4.11(m, 6H), 3.93-3.46(m, 4H), 2.77(m,

2H), 2.38-1.73(m, 6H), 1.40-1.25(m, 6H)

c) Synthesis of ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-(1R)-1-hydroxymethyl-2-oxoethyl]amino]acetate:

5

20mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 10mg of the title compound as a pale yellow solid.

10 ¹H NMR(MeOH-d₄, ppm) : δ 7.70(s, 1H), 7.38(m, 2H), 6.27(s, 1H), 4.21-4.14(m, 5H), 3.57-3.47(m, 6H), 3.22-2.72(m, 4H), 2.29-1.70(m, 6H), 1.35(t, 3H, J=7.09Hz), 1.25(t, 3H, J=7.14Hz)

ES-MS : 458(M+1)⁺

15 Example 50 : Synthesis of ethyl 4-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]-3-cyclopropylamino-4-oxobutanoate (Compound 72)

20 a) Synthesis of N-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]-N-cyclopropyl(1,1-dimethylethyloxy)methanamide:

25 375mg of 2-[2-((S)-1-2-chloroacetylpyrrolidin-2-yl)ethyl]-1-ethyl-indole-6-carbonitrile and 188mg of N-butyloxycarbonylcyclopropylamine were reacted under the same conditions as Example 45-b) to obtain 413mg of the title compound as a white solid.

30 ¹H NMR(CDCl₃, ppm) : δ 7.61-7.53(m, 2H), 7.30(m, 1H), 6.36(s, 1H), 4.31(brs, 1H), 4.15(q, 2H, J=7.28Hz), 3.93(brs, 2H), 3.54-3.37(m, 2H), 2.81-2.76(m, 3H), 2.58-1.75(m, 6H), 1.47(s, 9H), 1.35(t, 3H, J=7.28Hz), 0.75-0.62(m, 4H)

b) Synthesis of ethyl 4-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-3-[N-cyclopropyl-(1,1-dimethylethyloxy)carbonylamino]-4-oxobutanoate:

35

413mg of the compound obtained in the above a) was dissolved in 8ml of tetrahydrofuran and cooled to -78°C . To this solution was slowly added dropwise 0.489ml of 2M LDA (lithium diisopropylamide) solution. The reaction mixture was then stirred for 40 minutes. 0.108ml of ethyl bromoacetate was added dropwise thereto, and the mixture was stirred for 2 hours at -30°C . After 0.5ml of water was added dropwise, the reaction solution was evaporated under reduced pressure, diluted with 150 ml of dichloromethane, washed with 50ml of water, dried over sodium sulfate, and then filtered. The filtrate was evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:1)]. The fractions containing the pure desired product were combined and then evaporated under reduced pressure to obtain 167mg of the title compound as a white solid.

^1H NMR(CDCl_3 , ppm) : δ 7.59-7.54(m, 2H), 7.29(m, 1H), 6.37(s, 1H), 5.11(bris, 1H), 4.19-4.09(m, 5H), 3.64-3.33(m, 2H), 3.22-3.12(m, 1H), 2.78(t, 2H, $J=8.00\text{Hz}$), 2.61-2.52(m, 1H), 2.36-1.70(m, 7H), 1.47(s, 9H), 1.35(t, 3H, $J=7.19\text{Hz}$), 1.23(t, 3H, $J=7.10\text{Hz}$), 0.75-0.61(m, 4H)

c) Synthesis of ethyl 4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-3-(cyclopropylamino)-4-oxobutanoate:

165mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 33mg of the title compound as a pale yellow solid.

^1H NMR($\text{MeOH}-d_4$, ppm) : δ 7.77(s, 1H), 7.52-7.30(m, 2H), 6.33(s, 1H), 4.23-4.14(m, 3H), 4.01-3.84(m, 3H), 3.73-3.46(m, 2H), 2.85-2.48(m, 4H), 2.12-1.71(m, 7H), 1.29(t, 3H, $J=7.14\text{Hz}$), 1.11-1.05(m, 3H), 0.40-0.22(m, 4H)

ES-MS : 468($M+1$) $^+$

Example 51 : Synthesis of 4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-3-cyclopropylamino-4-oxobutanoic acid

(Compound 73)

26mg of ethyl 4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-3-cyclopropylamino-4-oxobutanoate was treated according to the same procedure as Example 44 to obtain 16mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.57(s, 1H), 7.31-7.06(m, 2H), 6.27(s, 1H), 4.22(brs, 1H), 4.13-4.05(m, 2H), 3.94-3.82(m, 2H), 3.74-3.66(m, 1H), 2.79-2.71(m, 2H), 2.46(m, 2H), 2.05-1.82(m, 7H), 1.22(t, 3H, J=7.13Hz), 0.36-0.31(m, 4H)

ES-MS : 440(M+1)⁺

Example 52 : Synthesis of ethyl 2-[2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]-N-cyclopentylacetylaminol]-acetate (Compound 75)

100mg of the compound I-b obtained in Example 2-b) and 98mg of ethyl 2-(2-chloro-N-cyclopentylacetylaminol)acetate were reacted under the same conditions as Example 42 to obtain the pale yellow solid product, which was then treated according to the same procedure as Example 1-n) to obtain 20mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.81-7.32(m, 3H), 6.31(m, 1H), 4.52-4.43(m, 1H), 4.04-3.96(m, 2H), 3.80-3.48(m, 4H), 3.85(s, 3H), 3.11-2.66(m, 4H), 2.55-1.03(m, 15H), 0.80(t, 3H, J=6.94Hz)

ES-MS : 482(M+1)⁺

Example 53 : Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylsulfonyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 77)

a) Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylsulfonyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

In a 25ml flask, 30mg of 1-methyl-2-((S)-2-pyrrolidin-2-ylethyl)-

indole-6-carbonitrile and 36mg of 2-naphthalenesulfonyl chloride were dissolved in 3ml of dichloromethane, and 0.055ml of triethylamine was added at room temperature. The reaction mixture was stirred for 2 hours, diluted with water and then extracted three times with dichloromethane. The extracts were combined, dried over MgSO₄ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the pure desired product were combined and then evaporated to obtain 26.9mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 8.26(s, 1H), 7.88(m, 2H), 7.78(m, 1H), 7.73(d, 1H), 7.70(m, 2H), 7.64(m, 1H), 7.59(m, 1H), 7.34(d, 1H), 6.39(s, 1H), 3.79(m, 1H), 3.74(s, 3H), 3.50(m, 1H), 3.34(m, 1H), 2.93(m, 2H), 2.28(m, 1H), 1.99(m, 1H), 1.83(m, 1H), 1.65(m, 2H), 1.58(m, 1H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-(2-naphthylsulfonyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

27mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 14mg of the title compound as a yellowish white solid.

¹H NMR(MeOH-d₄, ppm) : δ 8.11(s, 1H), 7.89-7.82(m, 3H), 7.64(d, 1H), 7.61-7.44(m, 4H), 7.43(d, 1H), 6.37(s, 1H), 3.77(s, 3H), 3.63(m, 1H), 3.37(m, 1H), 3.25(m, 1H), 2.85(m, 2H), 2.23(m, 1H), 1.91(m, 1H), 1.80(m, 1H), 1.59(m, 2H), 1.36(m, 1H),
ES-MS : 461(M+1)⁺

Example 54 : Synthesis of 1-methyl-2-[2-((S)-1-naphthylsulfonyl-pyrrolidin-2-yl)ethyl]indole-6-carboxamide (Compound 79)

a) Synthesis of 1-methyl-2-[2-((S)-1-naphthylsulfonylpyrrolidin-2-yl)-ethyl]indole-6-carbonitrile:

53mg of 1-naphthalenesulfonyl chloride was treated according to the same procedure as Example 53-a) to obtain 55mg of the title compound as a pale yellow solid.

5 ^1H NMR(CDCl_3 , ppm) : δ 8.79(d, 1H), 8.12(d, 1H), 7.98(d, 1H), 7.99(d, 1H), 7.54(m, 4H), 7.40(m, 1H), 7.32(m, 1H), 6.25(s, 1H), 3.99(m, 1H), 3.57(s, 3H), 3.47-3.40(m, 2H), 2.74(m, 2H), 2.11(m, 1H), 1.87-1.81(m, 3H), 1.66(m, 2H)

10 b) Synthesis of 1-methyl-2-[2-[(S)-1-naphthylsulfonylpyrrolidin-2-yl]-ethyl]indole-6-carboxamide:

51mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 25mg of the title compound as a yellowish white solid.

15 ^1H NMR($\text{MeOH}-d_4$, ppm) : δ 8.77(d, 1H), 8.06(m, 2H), 7.95(m, 2H), 7.67(d, 1H), 7.58(m, 1H), 7.52-7.40(m, 3H), 6.33(s, 1H), 3.94(m, 1H), 3.73(s, 3H), 3.50-3.42(m, 2H), 2.82(m, 2H), 2.14(m, 1H), 1.90(m, 2H), 1.74(m, 2H), 1.64(m, 1H)

Example 55 : Synthesis of 1-methyl-2-[2-((S)-1-acetylpyrrolidin-2-yl)ethyl]indole-6-carboxamide (Compound 81)

25 490mg of 1-methyl-2-[2-((S)-1-acetylpyrrolidin-2-yl)ethyl]indole-6-carbonitrile was treated according to the same procedure as Example 1-n) to obtain 24mg of the title compound.

30 ^1H NMR(CDCl_3 , ppm) : δ 7.99(s, 1H), 7.33(m, 2H), 6.12(s, 1H), 4.01(bs, 1H), 3.54(s, 3H), 3.45-3.20(m, 2H), 2.54(bs, 2H), 2.20-1.40(m, 6H), 1.97(s, 3H)

Example 56 : Synthesis of 1-methyl-2-[2-[(S)-1-(2-phenylsulfonyl-acetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 82)

a) Synthesis of 1-methyl-2-[2-[(S)-1-(2-phenylsulfonylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

70mg of the compound I-b obtained in Example 2-b) and 81mg of phenylsulfonylacetic acid were reacted according to the same procedure as Example 11-a) to obtain 12mg of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.94-7.91(m, 2H), 7.65(d, 1H, J=7.50Hz), 7.57-7.51(m, 4H), 7.29(d, 1H), 6.37(s, 1H), 4.23-4.10(m, 3H), 3.68(s, 3H), 3.75-3.66(m, 2H), 2.80(t, 3H, J=8.00Hz), 2.22-1.79(m, 6H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-(2-phenylsulfonylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

12mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 4mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.98-7.93(m, 3H), 7.74-7.62(m, 4H), 7.47(d, 1H, J=8.30Hz), 6.47(s, 1H), 4.15(bs, 1H), 3.82(s, 3H), 3.66-3.62(m, 2H), 3.33(s, 2H), 2.89(t, 2H), 2.20-1.84(m, 6H)

Example 57 : Synthesis of 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 83)

a) Synthesis of tert-butyl-(R)-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate:

17g of 1-ethyl-2-[(S)-pyrrolidin-2-yl]ethyl]indole-6-carbonitrile and 17.8g of (R)-N-(tert-butoxycarbonyl)proline were dissolved in dichloromethane, and 18.3g of WSCIHCl was added thereto. The reaction mixture was stirred for 2.5 hours at room temperature and, after water was added, extracted two times with dichloromethane. The extracts were combined, dried over MgSO₄ and then concentrated. The residue was purified with silica gel column chromatography [eluent:

dichloromethane/methanol(50:1)] to obtain 24g of the title compound as a white foam.

ES-MS : 465(M+1)⁺

5 ¹H NMR(CDCl₃, ppm) : δ 7.60-7.51(m, 2H), 7.32-7.24(m, 1H), 6.41-6.33(m, 1H), 4.52-4.47(m, 1H), 4.40-4.28(m, 1H), 4.16(q, J=7.20Hz, 2H), 3.79-3.62(m, 2H), 3.50-3.44(m, 2H), 2.83-2.79(m, 2H), 2.15-1.85(m, 10H), 1.43-1.40(m, 9H), 1.35(t, J=7.20Hz, 3H)

10 b) Synthesis of 1-ethyl-2-[2-[(S)-[1-((R)-pyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile (Compound II-a):

24g of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain 11g of the title compound as a white foam.

15 ¹H NMR(CDCl₃, ppm) : δ 7.60-7.56(m, 2H), 7.31-7.26(m, 1H), 6.43(s, 1H), 4.41-4.37(m, 1H), 4.20-4.13(m, 3H), 3.64-3.61(m, 1H), 3.41-3.34(m, 3H), 2.81-2.78(m, 2H), 2.43-2.38(m, 2H), 2.17-1.82(m, 8H), 1.38(t, J=7.20Hz, 3H)

c) Synthesis of 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

25 50mg of the compound II-a obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 27mg of the title compound as a pale yellow solid.

30 ¹H NMR(MeOH-d₄, ppm) : δ 7.81(s, 1H), 7.59-7.31(m, 2H), 6.39(s, 1H), 4.21-4.05(m, 3H), 3.68-3.46(m, 3H), 3.10-2.66(m, 4H), 2.27-1.52(m, 10H), 1.30(t, 3H, J=7.15Hz)

IR(KBr) cm⁻¹ : 3480, 1650, 1025

ES-MS : 382(M+1)⁺

35 Example 58 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate

(Compound 84)

a) Synthesis of 1-methyl-2-[(2S)-[1-((2R)-pyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile (Compound II-b):

300mg of the compound I-b obtained in Example 2-b) was treated according to the same procedure as Examples 57-a) and 57-b) to obtain 200mg of the title compound as a white foam.

¹H NMR(CDCl₃, ppm) : δ 7.63(s, 1H), 7.38(d, 1H), 7.10(d, 1H), 6.30(s, 1H), 4.25(t, 3H), 4.10-4.00(m, 1H), 3.65(s, 3H), 3.45-3.20(m, 2H), 2.80-2.70(m, 2H), 2.45-2.30(m, 1H), 2.30-2.15(m, 1H), 2.1-1.6(m, 1H)

b) Synthesis of methyl 2-[(R)-2-[(S)-2-[2-(6-cyano-1-methylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

50.0mg of the compound II-b obtained in the above a) was dissolved in dichloromethane and then cooled to 0°C. 24μl of triethylamine was added thereto, and after 20 minutes, 16μl of methyl bromoacetate was added dropwise. After 20 minutes, water was added and the reaction solution was extracted two times with dichloromethane. The extracts were combined, dried over MgSO₄ and then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 28mg of the title compound as a colorless liquid.

¹H NMR(CDCl₃, ppm) : δ 7.56-7.48(m, 2H), 7.32(m, 1H), 6.44(s, 1H), 4.28-4.15(bs, 1H), 3.86(m, 1H), 3.72(s, 3H), 3.67(s, 3H), 3.50(m, 2H), 2.82(m, 4H), 2.37-1.60(m, 12H)

c) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

26mg of the compound obtained in the above b) was dissolved in 15ml of ethanol solution saturated with HCl gas. The reaction solution

was allowed to stand at room temperature for one day and then concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vacuum pump. The dried product was then dissolved in 15ml of ethanol solution saturated with NH₃ gas. After one day, the reaction solution was concentrated under reduced pressure. The residue was purified with column chromatography [eluent: ethyl acetate/methanol(1:1)] on NH-DM1020 silica to obtain 12mg of the title compound as a yellowish white solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.94(s, 1H), 7.68(d, 1H), 7.47(d, 1H), 6.52(s, 1H), 4.30(bs, 1H), 3.92(m, 1H), 3.80-3.50(m, 7H), 3.28(m, 1H), 3.15-2.90(m, 3H), 2.40-1.75(m, 12H), 1.25(t, 3H)

Example 59 : Synthesis of ethyl 2-[(R)-2-[[2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]azetidiny]carbonyl]pyrrolidiny]acetate (Compound 85)

a) Synthesis of methyl (S)-2-azetidine carboxylate:

900mg of azetidine-(S)-2-carboxylic acid was treated according to the same procedure as Example 1-g) to obtain 1g of the title compound as a colorless oil.

b) Synthesis of methyl (S)-2-(tert-butoxycarbonyl)-2-azetidine carboxylate:

1g of the compound obtained in the above a) was treated according to the same procedure as Example 1-h) to obtain 1.8g of the title compound as a colorless oil.

¹H NMR(CDCl₃, ppm) : δ 4.61(m, 1H), 4.02(m, 1H), 3.89(m, 1H), 3.77(s, 3H), 2.50(m, 1H), 2.17(m, 1H), 1.42(s, 9H)

c) Synthesis of tert-butyl (S)-2-formylazetidine carboxylate:

1.7g of the compound obtained in the above b) was treated according to the same procedure as Example 1-i) to obtain 1.4g of the title compound as a colorless oil.

5 ^1H NMR(CDCl_3 , ppm) : δ 4.45(m, 1H), 3.92-3.77(m, 2H), 3.50(m, 1H),
2.30-2.08(m, 2H), 1.42(s, 9H)
ES-MS : 187(M+2)⁺

10 d) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)vinyl]azetidine carboxylate:

3.8g of 6-cyano-1-ethylindole-2-methyl triphenylphosphonium bromide and 1.3g of tert-butyl (S)-2-formylazetidine carboxylate obtained in the above c) were treated according to the same procedure as Example
15 1-j) to obtain 1.7g of the title compound as a pale yellow solid.

^1H NMR(CDCl_3 , ppm) : δ 7.60(m, 2H), 7.28(m, 1H), 6.70(s, 1H), 6.61(s,
1H), 6.55(d, 1H), 4.88(m, 1H), 4.21(q, 2H, J=7.2Hz), 3.92(m, 2H),
2.49(m, 1H), 2.10(m, 1H), 1.43(m, 9H), 1.38(m, 3H)

20

e) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-
azetidine carboxylate:

1.6g of the compound obtained in the above d) was treated
25 according to the same procedure as Example 1-k) to obtain 1.2g of the
title compound as a yellow oil.

^1H NMR(CDCl_3 , ppm) : δ 7.59(m, 2H), 7.28(m, 1H), 6.35(s, 1H), 4.36(m,
1H), 4.14(q, 2H, J=7.2Hz), 3.86(m, 2H), 2.83(m, 2H), 2.33(m, 2H),
30 2.10(m, 1H), 1.92(m, 1H), 1.46(s, 9H), 1.35(t, 3H, J=7.2Hz)

f) Synthesis of 2-[2-((S)-2-azetidiny)ethyl]-1-ethylindole-6-carbonitrile:

1.1g of the compound obtained in the above e) was treated
35 according to the same procedure as Example 1-l) to obtain 0.75g of the

title compound as a pale yellow solid.

g) Synthesis of tert-butyl (R)-2-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]azetidiny]carbonyl]pyrrolidine carboxylate:

5

730mg of the compound obtained in the above f) was treated according to the same procedure as Example 11-a) to obtain 920mg of the title compound as a yellowish white oil.

10 ¹H NMR(CDCl₃, ppm) : δ 7.54(m, 2H), 7.28(m, 1H), 6.35(s, 1H), 4.54(m, 1H), 4.10(m, 3H), 3.53(m, 1H), 2.93(m, 1H), 2.48(m, 1H), 2.30(m, 2H), 2.07(m, 4H), 1.87(m, 2H), 1.44(s, 9H), 1.35(t, 3H, J=7.1Hz)

15 h) Synthesis of 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)-2-azetidiny]ethyl]indole-6-carbonitrile:

900mg of the compound obtained in the above g) was treated according to the same procedure as Example 1-l) to obtain 660mg of the title compound as a pale yellow solid.

20

¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.29(m, 1H), 6.35(s, 1H), 4.53(m, 1H), 4.15(q, 2H, J=7.1Hz), 4.04(m, 1H), 3.63(m, 1H), 3.20(m, 1H), 2.88(m, 3H), 2.49(m, 2H), 2.02(m, 3H), 1.82(m, 2H), 1.70(m, 1H), 1.36(t, 3H, J=7.1Hz)

25

i) Synthesis of ethyl 2-[(R)-2-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]azetidiny]carbonyl]pyrrolidiny]acetate:

650mg of the compound obtained in the above h) and 0.31ml of ethyl 2-bromoacetate were treated according to the same procedure as Example 1-m) to obtain 690mg of the title compound as a pale yellow oil.

30 ¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.29(m, 1H), 6.36(s, 1H), 4.55(m, 1H), 4.16(m, 5H), 3.51(m, 2H), 3.20(m, 1H), 2.92-2.75(m, 3H), 2.46(m, 2H), 2.09(m, 2H), 1.92(m, 4H), 1.36(t, 3H, J=7.1Hz), 1.25

35

(m, 3H)

j) Synthesis of ethyl 2-[(2)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]azetidiny]carbonyl]pyrrolidiny]acetate:

5

680mg of the compound obtained in the above i) was treated according to the same procedure as Example 1-n) to obtain 90mg of the title compound as a pale yellow solid.

10 ^1H NMR(CDCl_3 , ppm) : δ 7.61(m, 1H), 7.53(m, 1H), 7.32(m, 1H), 6.33(s, 1H), 5.08-4.65(br, 2H), 4.54(m, 1H), 4.17(m, 5H), 3.69(m, 1H), 3.48(m, 2H), 3.41(m, 1H), 3.19(m, 1H), 2.88-2.73(m, 3H), 2.45(m, 2H), 2.13(m, 2H), 1.90(m, 4H), 1.36(t, 3H), 1.24(t, 3H)

IR(KBr) : 3250, 2900, 1720, 1620, 1460 cm^{-1}

15 ES-MS : 454(M+1) $^+$, 477(M+Na)

Example 60 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidiny]carbonyl]pyrrolidiny]acetate (Compound 86)

20

a) Synthesis of methyl 2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidiny]carbonyl]pyrrolidiny]acetate:

615mg of the compound II-a obtained in Example 57-b) was dissolved in dichloromethane, and 0.39ml of triethylamine was added thereto at room temperature. After 20 minutes, 280mg of methyl bromoacetate was added dropwise thereto. After 20 minutes, water was added and the reaction mixture was extracted three times with dichloromethane. The extracts were combined, dried over MgSO_4 and then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(50:1)] to obtain 406mg of the title compound as a colorless liquid.

30 ^1H NMR(CDCl_3 , ppm) : δ 7.60-7.47(m, 2H), 7.29(s, 1H), 6.44(s, 1H), 4.25 (bs, 1H), 4.20-4.10(m, 2H), 3.83(bs, 1H), 3.67(s, 3H), 3.60-3.43

35

(m, 2H), 3.25-3.17(m, 1H), 2.88-2.72(m, 3H), 2.38-1.62(m, 12H), 1.36(t, 3H)

5 b) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate :

406mg of the compound obtained in the above a) was dissolved in 30ml of ethanol solution saturated with HCl gas. The reaction solution was allowed to stand at room temperature for 2 days and then concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vacuum pump. The dried product was then dissolved in 30ml of ethanol solution saturated with NH₃ gas. After 2 days, the reaction solution was concentrated under reduced pressure and the residue thereby obtained was purified with column chromatography [eluent: ethyl acetate/methanol(1:1)] on NH-DM1020 silica to obtain 246mg of the title compound as a white foamy solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.88(s, 1H), 7.57(d, 1H), 7.40(d, 1H), 6.47(s, 1H), 4.43-4.18(m, 3H), 4.18-4.03(m, 2H), 3.78(m, 1H), 3.74-3.45(m, 4H), 2.70(m, 2H), 2.12-1.60(m, 12H), 1.35(t, 3H), 1.18(t, 3H)

Example 61 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]piperidyl]carbonyl]pyrrolidinyl]acetate (Compound 87)

25 a) Synthesis of tert-butyl (S)-2-(methoxycarbonyl)piperidine carboxylate:

In a 100ml flask, 5g of 1-((tert-butyl)oxycarbonyl)piperidine-(S)-2-carboxylic acid and 3.2g of NaHCO₃ were dissolved in 50ml of N,N-dimethylformamide, and 1.8ml of iodomethane was added thereto. The reaction solution was stirred for 8 hours at room temperature. After adding water, the reaction solution was extracted two times with ethyl acetate. The extracts were combined, dried over MgSO₄ and evaporated to obtain 4.5g of the title compound as a pale yellow oil.

¹H NMR(CDCl₃, ppm) : δ 4.94-4.73(brs, 1H), 3.97(br, 1H), 3.73(s, 3H), 2.95-2.88(br, 1H), 2.21(m, 1H), 1.65(m, 3H), 1.45(br, 9H), 1.25(m, 2H)

5 b) Synthesis of tert-butyl (S)-2-formylpiperidine carboxylate:

3g of tert-butyl (S)-2-(methoxycarbonyl)piperidine carboxylate obtained in the above a) was treated according to the same procedure as Example 1-i) to obtain 2g of the title compound as a colorless oil.

10

¹H NMR(CDCl₃, ppm) : δ 9.59(s, 1H), 4.58(br, 1H), 4.08-3.89(br, 1H), 2.91(br, 1H), 2.14(m, 1H), 1.66(m, 3H), 1.46(br, 9H), 1.25(m, 2H)

15 c) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)vinyl]-piperidine carboxylate:

4g of 6-cyano-1-ethylindole-2-methyl triphenylphosphonium bromide and 1.9g of tert-butyl (S)-2-formylpiperidinecarboxylate obtained in the above b) were treated according to the same procedure as Example 1-m) to obtain 1.8g of the title compound as a pale yellow solid.

20

¹H NMR(CDCl₃, ppm) : δ 7.60(m, 2H), 7.29(m, 1H), 6.62(m, 1H), 6.43(m, 1H), 6.27(m, 1H), 5.39(m, 1H), 4.18(m, 2H), 4.11(m, 1H), 2.99(m, 1H), 1.79(m, 2H), 1.69(m, 2H), 1.48(m, 2H), 1.34(m, 3H), 1.25(m, 9H)

25

ES-MS : 380(M+1)⁺

d) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-piperidine carboxylate:

30

1.5g of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 1.5g of the title compound as a brown oil.

35 ¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.27(m, 1H), 6.35(s, 1H), 4.41(br,

1H), 4.15(m, 2H), 4.02(m, 1H), 2.68(m, 3H), 2.16(m, 1H), 1.83(m, 1H), 1.67-1.61(br, 6H), 1.45(s, 9H), 1.35(t, 3H, J=7.2Hz)

e) Synthesis of 1-ethyl-2-[2-(2-piperidyl)ethyl]indole-6-carbonitrile:

5

1.5g of the compound obtained in the above d) was treated according to the same procedure as Example 1-1) to obtain 1.1g of the title compound as a pale yellow solid.

10 ¹H NMR(CDCl₃, ppm) : δ 7.47(m, 2H), 7.28(m, 1H), 6.31(s, 1H), 4.63-4.51(br, 1H), 4.11(q, 2H, J=7.2Hz), 3.18(m, 1H), 2.80(m, 3H), 1.95-1.85(m, 4H), 1.62(m, 1H), 1.40(m, 3H), 1.31(t, 3H, J=7.2Hz)
ES-MS : 282(M+1)⁺

15 f) Synthesis of tert-butyl (R)-2-[[2-(2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]piperidyl)carbonyl]pyrrolidine carboxylate:

1.1g of the compound obtained in the above e) was treated according to the same procedure as Example 11-a) to obtain 860mg of the title compound as a pale brown oil.

20 ¹H NMR(CDCl₃, ppm) : δ 7.54(m, 2H), 7.26(m, 1H), 6.33(s, 1H), 4.98(m, 1H), 4.64(m, 1H), 4.16(m, 2H), 3.78(m, 1H), 3.57(m, 1H), 3.47(m, 1H), 3.21(m, 1H), 2.74(m, 2H), 1.88(m, 3H), 1.73-1.64(br, 5H), 1.45(m, 9H), 1.38(m, 3H)
25 ES-MS : 479(M+1)⁺

g) Synthesis of 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)-2-piperidyl]ethyl]indole-6-carbonitrile:

30

670mg of the compound obtained in the above f) was treated according to the same procedure as Example 1-1) to obtain 440mg of the title compound as a pale yellow solid.

35 h) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-

ethyl]piperidyl]carbonyl]pyrrolidinyl]acetate:

430mg of the compound obtained in the above g) and 0.19ml of ethyl 2-bromoacetate were treated according to the same procedure as
5 Example 1-m) to obtain 320mg of the title compound as a pale brown oil.

¹H NMR(CDCl₃, ppm) : δ 7.53(m, 2H), 7.29(m, 1H), 6.36(s, 1H), 4.98(br, 1H), 4.12(m, 5H), 3.92(m, 2H), 3.59(m, 2H), 3.23(m, 1H), 3.06(m, 1H), 2.79-2.62(m, 4H), 2.16(m, 3H), 1.91-1.85(br, 5H), 1.28(m, 3H), 1.21(m, 3H)

ES-MS : 465(M+1)⁺

i) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]piperidyl]carbonyl]pyrrolidinyl]acetate :

300mg of the compound obtained in the above h) was treated according to the same procedure as Example 1-n) to obtain 60mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.88(s, 1H), 7.52(m, 1H), 7.30(m, 1H), 6.32(s, 1H), 4.97(br, 1H), 4.14(m, 4H), 3.93(m, 1H), 3.26(m, 1H), 3.11(m, 1H), 2.74(m, 2H), 2.18(br, 2H), 1.86(m, 4H), 1.67(br, 6H), 1.33(m, 3H), 1.23(m, 3H)

IR(KBr) : 3430, 2900, 1640 cm⁻¹

ES-MS : 482(M+1)⁺

Example 62 : Synthesis of 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetic acid (Compound 88)

720mg of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate was treated according to the same procedure as Example 44 to obtain 583mg of the title compound as a white solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.83(s, 1H), 7.55(d, 1H, J=8.34Hz), 7.25(d, 1H, J=8.36Hz), 6.36(s, 1H), 4.25-4.03(m, 3H), 3.62(m, 1H), 3.52-3.38(m, 2H), 3.16-3.03(m, 2H), 2.73(m, 2H), 2.37-1.46(m, 12H), 1.24(t, 3H)

5 ES-MS : 440(M+1)⁺

IR(KBr) : 3200, 1600 cm⁻¹

Example 63 : Synthesis of 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]piperidyl]carbonyl]pyrrolidinyl]acetic acid
 10 (Compound 89)

In a 50ml flask, 140mg of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]piperidyl]carbonyl]pyrrolidinyl]acetate was dissolved in 10ml of ethanol, and 0.5ml of 2N NaOH was added thereto. The reaction solution was stirred for 3 hours at room temperature and evaporated under reduced pressure to remove the solvent. The residue was purified with column chromatography [eluent: ethyl acetate/methanol (1:1)] on NH-DM1020 silica to obtain 60mg of the title compound as a yellowish white solid.

20

¹H NMR(MeOH-d₄, ppm) : δ 7.87(m, 1H), 7.59(m, 1H), 7.42(m, 1H), 6.42(m, 1H), 4.25(m, 2H), 3.64(m, 1H), 3.20(m, 1H), 3.15(m, 1H), 2.78(m, 2H), 2.31(m, 2H), 1.91(br, 2H), 1.77-1.68(br, 6H), 1.36(m, 3H)

25 IR(KBr) : 3400, 3000, 1650, 1600 cm⁻¹

ES-MS : 454(M+1)⁺, 476(M+Na), 498(M+2Na)

Example 64 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-(S)-4-methylpyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 97)
 30

a) Synthesis of (R)-4-hydroxy-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid:

35

In a 1 l flask, 25g of (R)-4-hydroxy-L-proline was dissolved in

350ml of 4N-NaOH solution and then cooled to -20°C . To the resulting solution was added dropwise 41ml of benzyl chloroformate, and the reaction mixture was stirred for one hour at -20°C . After the reaction is completed, the reaction solution was adjusted to pH 4 with 2N aqueous HCl solution and then extracted two times with ethyl acetate. The organic layers were combined, dried over MgSO_4 and evaporated to obtain 31.5g of the title compound as a white solid.

b) Synthesis of (S)-4-oxo-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid:

In a 500ml flask, 37.2g of CrO_3 and a small quantity of ice-water were mixed and 30.8ml of concentrated sulfuric acid was added dropwise thereto. The resulting solution was diluted with water to prepare 140ml of 8N-chromic acid. In a 2 l flask, 31.5g of the compound obtained in the above a) was dissolved in 800ml of acetone, and 140ml of 8N-chromic acid as prepared above was slowly added thereto. The reaction mixture was stirred for 2 hours at room temperature, and methanol was added dropwise to complete the reaction. The resulting precipitate was filtered and the filtrate was evaporated. The residue was extracted two times with chloroform. The organic layers were combined, dried over MgSO_4 and then evaporated to obtain 28.4g of the title compound as a white solid.

^1H NMR(CDCl_3 , ppm) : δ 10.0(br, 1H), 7.30(s, 5H), 5.15(m, 2H), 4.90(m, 1H), 5.95(m, 2H), 2.95(m, 1H), 2.65(m, 1H)

ES-MS : 264(M+1) $^+$

c) Synthesis of phenylmethyl (S)-4,4-dimethoxy-2-(methoxycarbonyl)-pyrrolidine carboxylate:

In a 100ml flask, 4.0g of the compound obtained in the above b) was dissolved in 40ml of methanol, and 1.08ml of thionyl chloride was slowly added thereto at 0°C . The reaction mixture was refluxed for 2 hours with stirring. After the reaction was completed, the reaction

solution was evaporated under reduced pressure. The residue was extracted twice with ethyl acetate. The organic layers were combined, dried over MgSO_4 and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:2)].
5 The fractions containing the desired product were combined and evaporated to obtain 4.2g of the title compound as a colorless liquid.

^1H NMR(CDCl_3 , ppm) : δ 7.30(m, 5H), 5.30-5.0(m, 2H), 4.45(m, 1H), 3.80
(s, 2H), 3.55(m, 3H), 3.15(s, 6H), 2.35(m, 1H), 2.20(m, 1H)
10 ES-MS : 324(M+1) $^+$

d) Synthesis of methyl (S)-4-oxo-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylate:

15 In a 100ml flask, 3.0g of the compound obtained in the above c) was dissolved in 90ml of acetone and $\text{TsOH} \cdot \text{H}_2\text{O}$ was then added. The reaction mixture was refluxed for 2 hours with stirring. After the reaction was completed, the reaction solution was evaporated under reduced pressure, and the residue was extracted twice with ethyl acetate.
20 The organic layers were combined, dried over MgSO_4 and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:2)]. The fractions containing the desired product were combined and evaporated to obtain 3.2g of the title compound as a colorless liquid.

25 ^1H NMR(CDCl_3 , ppm) : δ 7.35(m, 5H), 5.20(m, 2H), 4.80(m, 1H), 4.0(s, 2H), 3.80(d, 3H), 2.95(m, 1H), 2.55(dd, 1H, $J=18.85\text{Hz}$, 2.67Hz)
ES-MS : 278(M+1) $^+$

30 e) Synthesis of methyl (S)-4-methylene-1-(benzyloxycarbonyl)pyrrolidine carboxylate:

In a 100ml flask, 10.0g of methyltriphenylphosphonium bromide was dissolved in 50ml of tetrahydrofuran, and $t\text{BuOK}$ was slowly added
35 thereto. The reaction mixture was stirred for 2 hours. 3.11g of the

compound obtained in the above d) which was dissolved in a small quantity of tetrahydrofuran was slowly added dropwise, and the mixture was stirred for 2 hours. After the reaction was quenched with a small quantity of water, the reaction solution was evaporated under reduced pressure, and the residue was extracted twice with ethyl ether. The organic layers were combined, dried over MgSO_4 and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:5)]. The fractions containing the desired product were combined and evaporated to obtain 1.5g of the title compound as a colorless liquid.

^1H NMR(CDCl_3 , ppm) : δ 7.35(br, 5H), 5.20(m, 2H), 5.0(br, 2H), 4.55(m, 1H), 4.15(br, 2H), 3.65(d, 3H), 3.0(m, 1H), 2.65(d, 1H, $J=16.0\text{Hz}$)
ES-MS : 276(M+1) $^+$

f) Synthesis of methyl (S)-4-methyl-1-[tert-butoxycarbonyl]pyrrolidine-2-carboxylate:

1.5g of the compound obtained in the above e) was treated according to the same procedure as Example 1-k) to obtain 540mg of the yellow liquid product, which was then treated according to the same procedure as Example 1-h) to obtain 887mg of the title compound as a yellow liquid.

^1H NMR(CDCl_3 , ppm) : δ 4.20(m, 2H), 3.70(br, 3H), 3.0(t, 1H, $J=10.05\text{Hz}$), 2.40(m, 1H), 2.20(m, 1H), 1.50-1.30(br, 9H), 1.20(m, 1H), 1.0(br, 3H)
ES-MS : 244(M+1) $^+$

g) Synthesis of tert-butyl (S)-2-formyl-(S)-4-methylpyrrolidine carboxylate:

880mg of the compound obtained in the above f) was treated according to the same procedure as Example 1-i) to obtain the title compound as a yellow liquid in a quantitative yield.

h) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)vinyl]-(S)-4-methylpyrrolidine carboxylate:

2.85g of 6-cyano-1-ethylindole-2-ethyl triphenylphosphonium bromide obtained in Example 1-f) and the compound obtained in the above g) were treated according to the same procedure as Example 1-j) to obtain 800mg of the title compound as a yellow fluorescent liquid.

¹H NMR(CDCl₃, ppm) : δ 7.60(m, 2H), 7.25(m, 1H), 6.65(s, 1H), 6.60-6.40(br, 1H), 6.25(dd, 1H, J=15.63Hz, 6.89Hz), 4.40(m, 1H), 4.20(q, 2H, J=7.24Hz), 4.0-3.45(m, 2H), 2.45-2.10(m, 2H), 1.60-1.30(m, 12H), 1.25(m, 1H), 1.05(d, 3H, J=6.51Hz)

ES-MS : 380(M+1)⁺

i) Synthesis of tert-butyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-(S)-4-methylpyrrolidine carboxylate:

800mg of the compound obtained in the above h) was treated according to the same procedure as Example 1-k) to obtain 710mg of the title compound as a colorless liquid.

¹H NMR(CDCl₃, ppm) : δ 7.55(m, 2H), 7.25(m, 1H), 6.30(s, 1H), 4.15(q, 2H, J=7.24Hz), 3.90-3.60(m, 2H), 2.70(m, 3H), 2.30(m, 2H), 2.10(m, 1H), 1.85(m, 1H), 1.45(s, 9H), 1.35(t, 3H, J=7.24Hz), 1.25(m, 1H), 1.10(d, 3H, J=6.46Hz)

ES-MS : 382(M+1)⁺

j) Synthesis of 1-ethyl-2-[2-[(S)-((S)-4-methylpyrrolidin-2-yl)ethyl]-indole-6-carbonitrile:

30

430mg of the compound obtained in the above i) was treated according to the same procedure as Example 1-l) to obtain 401mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.45(m, 2H), 7.25(m, 1H), 6.25(s, 1H), 4.05(q,

35

2H, J=7.24Hz), 3.60(m, 2H), 3.35(m, 1H), 2.90-2.65(m, 3H),
2.40-2.20(m, 3H), 2.15(m, 1H), 1.25(t, 3H, J=7.24Hz), 1.10(d, 3H,
J=6.46Hz)

ES-MS : 282(M+1)⁺

5

k) Synthesis of tert-butyl (R)-2-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-
ethyl]-(S)-4-methylpyrrolidinyl]carbonyl]pyrrolidine carboxylate:

400mg of the compound obtained in the above j) was treated
according to the same procedure as Example 11-a) to obtain 370mg of the
title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.55(m, 2H), 7.25(m, 1H), 6.30(m, 1H), 4.40(m,
1H), 4.10(m, 2H), 3.60(m, 2H), 3.40(m, 1H), 3.10(m, 1H), 2.80(m,
3H), 2.60-1.80(m, 6H), 1.80-1.10(m, 13H, J=6.46Hz), 1.05(d, 3H,
J=6.46Hz)

15

ES-MS : 479(M+1)⁺

l) Synthesis of 1-ethyl-2-[2-[(S)-4-methyl-1-((R)-pyrrolidin-2-ylcarbo-
nyl)pyrrolidin-(S)-2-yl]ethyl]indole-6-carbonitrile:

20

270mg of the compound obtained in the above k) was treated
according to the same procedure as Example 1-l) to obtain 220mg of the
title compound as a pale yellow solid.

25

¹H NMR(CDCl₃, ppm) : δ 7.55(m, 2H), 7.25(m, 1H), 6.40(s, 1H), 4.15(q,
2H, J=7.24Hz), 3.80(m, 1H), 3.25(m, 1H), 3.0(m, 2H), 2.80(m, 2H),
2.50(m, 1H), 2.20(m, 2H), 2.0-1.60(m, 4H), 1.50-1.20(m, 4H), 1.05
(d, 3H, J=6.46Hz)

ES-MS : 379(M+1)⁺

30

m) Synthesis of 1-ethyl-2-[2-[(S)-4-methyl-1-((R)-pyrrolidin-2-ylcarbo-
nyl)pyrrolidin-(S)-2-yl]ethyl]indole-6-carbonitrile:

150mg of the compound obtained in the above l) was treated

35

according to the same procedure as Example 1-m) to obtain 247mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.55(m, 2H), 7.25(m, 1H), 6.40(s, 1H), 4.20-4.00
5 (m, 4H), 3.95-3.75(m, 2H), 3.50(q, 2H), 3.20(m, 1H), 3.0-2.70(m, 4H), 2.60(m, 1H), 2.35(m, 1H), 2.20-1.70(m, 7H), 1.35(t, 3H, J=7.22Hz), 1.25(m, 4H), 1.10(d, 3H, J=6.43Hz)

ES-MS : 466(M+1)⁺

10 n) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]]-(S)-4-methylpyrrolidinyl]carbonyl]pyrrolidinylacetate :

240mg of the compound obtained in the above m) was treated according to the same procedure as Example 1-n) to obtain 71mg of the
15 title compound as a pale yellow solid.

¹H NMR(CDCl₃) : δ 7.80(s, 1H), 7.50(d, 1H), 7.40(d, 1H), 6.40(s, 1H),
4.30-4.10(m, 4H), 3.90-3.70(m, 2H), 3.50(q, 2H), 3.20(m, 1H),
3.0-2.65(m, 4H), 2.60(m, 1H), 2.30(m, 1H), 2.20-1.70(m, 7H),
20 1.35(t, 3H, J=7.08Hz), 1.25(t, 3H, J=7.11Hz), 1.05(d, 3H, J=6.41Hz)

ES-MS : 482(M+1)⁺

IR(KBr) : 3100, 2950, 1750, 1650 cm⁻¹

25 Example 65 : Synthesis of 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]]-(S)-4-methylpyrrolidinyl]carbonyl]pyrrolidinylacetic acid (Compound 98)

42mg of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]]-(S)-4-methylpyrrolidinyl]carbonyl]pyrrolidinylacetate obtained in
30 Example 64 was treated according to the same procedure as Example 44 to obtain 27mg of the title compound as a pale yellow solid.

¹H NMR(CD₃OD, ppm) : δ 7.70(s, 1H), 7.40(d, 1H), 7.20(d, 1H), 6.25(s, 1H),
35 4.20-3.80(m, 3H), 3.65(m, 1H), 3.15-2.50(m, 6H), 2.50-1.40

(m, 9H), 1.15(m, 3H), 0.95(m, 3H)

ES-MS : 454(M+1)⁺

IR(KBr) : 3200, 2950, 2850, 1650 cm⁻¹

5 Example 66 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-
1-ethylindol-2-yl)ethyl]-(S)-4-methoxypyrrolidinyl]carbonyl]pyrro-
lidinyl]acetate (Compound 99)

10 a) Synthesis of (4R)-4-hydroxy-1-(benzyloxycarbonyl)pyrrolidine-(S)-2-
carboxylic acid:

15 In a 250ml flask, 10g of (R)-4-hydroxypyrrolidine-(S)-2-
carboxylic acid and 140ml of 4N NaOH were introduced and cooled to -20
°C, and 17ml of benzyl chloroformate was slowly added. The reaction
solution was stirred for one hour at -20°C and extracted with ethyl ether
and water. The ether layer was removed and the aqueous layer was
acidified with 2N aqueous HCl solution and then extracted twice with
ethyl acetate. The extracts were combined, dried over MgSO₄ and then
evaporated to obtain 17.3g of the title compound as a colorless oil.

20 ¹H NMR(CDCl₃, ppm) : δ 7.30(m, 5H), 5.17(m, 2H), 4.52(m, 1H), 4.45(m,
1H), 3.60(m, 2H), 2.24(m, 2H)

25 b) Synthesis of 4-oxo-1-(benzyloxycarbonyl)pyrrolidine-(S)-2-carboxylic
acid:

30 In a 1 l flask, 16g of the compound obtained in the above a) was
dissolved in 600ml of acetone, and 64ml of 8N chromic acid was then
slowly added at -10°C. The reaction mixture was stirred for 4 hours at
-10°C, and 40ml of methanol was added thereto. The reaction solution
was filtered. To the filtrate was added water, and the mixture was
extracted twice with chloroform. The extracts were combined, dried
over MgSO₄ and evaporated. The residue was purified with silica gel
column chromatography [eluent: dichloromethane/methanol(10:1)] to obtain
35 12g of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.34(s, 5H), 5.16(m, 1H), 5.09(m, 1H), 4.69(m, 1H), 3.92(s, 2H), 2.87(m, 1H), 2.64(m, 1H)

ES-MS : 264(M+1)⁺

5

c) Synthesis of (S)-4-hydroxy-1-(benzyloxycarbonyl)pyrrolidine-(S)-2-carboxylic acid:

In a 250ml flask, 4.6g of the compound obtained in the above b) was dissolved in 164ml of methanol, and 2.6g of NaBH₄ dissolved in 11ml of water was slowly added at -10°C. The reaction solution was stirred for about 2.5 hours at -10°C to 0°C and then evaporated to remove methanol. About 100ml of 2N aqueous NaOH solution was added to the residue and then stirred for 30 minutes at room temperature. The reaction solution was cooled to 0°C, acidified with hydrochloric acid and then extracted twice with ethyl acetate. The extracts were combined, dried over MgSO₄ and evaporated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(3:1)] to obtain 3.2g of the title compound as a yellowish white solid.

20

¹H NMR(CDCl₃, ppm) : δ 7.30(m, 5H), 6.90(br, 1H), 5.12(m, 2H), 4.43(m, 2H), 3.64(m, 1H), 3.54(m, 1H), 2.21(br, 2H)

ES-MS : 266(M+1)⁺

25 d) Synthesis of (S)-4-methoxy-1-(benzyloxycarbonyl)pyrrolidine-(S)-2-carboxylic acid:

In a 100ml flask, 3g of the compound obtained in the above c) was dissolved in 40ml of tetrahydrofuran, and 0.95g of 60% NaH was slowly added. The reaction solution was stirred for one hour at room temperature, and 1.48ml of iodomethane was added. The reaction mixture was stirred for 3 hours at refluxing temperature and then for 10 hours at room temperature, and evaporated. To the residue was added water, and the mixture was acidified with 2N HCl and extracted twice with dichloromethane. The extracts were combined, dried over MgSO₄

35

and then evaporated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(3:1)] to obtain 3.2g of the title compound as a pale brown oil.

- 5 ^1H NMR(CDCl_3 , ppm) : δ 7.31(m, 5H), 5.17(m, 2H), 4.46(m, 1H), 3.94(m, 1H), 3.64(m, 2H), 3.26(s, 3H), 2.45-2.38(m, 1H), 2.22(m, 1H)
ES-MS : 280(M+1)⁺, 302(M+Na)

- 10 e) Synthesis of phenylmethyl (S)-4-methoxy-(S)-2-(methoxycarbonyl)-pyrrolidine carboxylate:

In a 100ml flask, 13ml of methanol was introduced and 0.93ml of thionyl chloride was slowly added thereto at 0°C. 3.1g of the compound obtained in the above d) which was dissolved in 11ml of methanol was
15 added thereto, and the reaction mixture was stirred for 2 hours at refluxing temperature and then evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate (3:1)] to obtain 2.4g of the title compound as a colorless oil.

- 20 ^1H NMR(CDCl_3 , ppm) : δ 7.31(m, 5H), 5.17(m, 2H), 4.45(m, 1H), 3.93(m, 1H), 3.72(m, 2H), 3.67(s, 3H), 3.25(s, 3H), 2.32-2.22(m, 2H)
ES-MS : 294(M+1)⁺

- 25 f) Synthesis of phenylmethyl (S)-2-formyl-(S)-4-methoxypyrrolidine carboxylate:

2.3g of the compound obtained in the above e) was treated according to the same procedure as Example 1-i) to obtain 1.4g of the
30 title compound as a colorless oil.

- ^1H NMR(CDCl_3 , ppm) : δ 7.33(m, 5H), 5.16(m, 2H), 4.19(m, 1H), 3.92(m, 1H), 3.73(m, 1H), 3.52(m, 1H), 3.22(s, 3H), 2.38(m, 1H), 2.14(m, 1H)
35 ES-MS : 264(M+1)⁺

g) Synthesis of phenylmethyl (S)-2-[2-(6-cyano-1-ethylindol-2-yl)vinyl]-
-(S)-4-methoxypyrrolidine carboxylate:

2.3g of 6-cyano-1-ethylindole-2-methyl triphenylphosphonium
5 bromide and 1.2g of phenylmethyl 2-formyl-4-methoxypyrrolidine carboxylate were reacted according to the same procedure as Example 1-j) to obtain 1.7g of the title compound as a yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.58(br, 2H), 7.36-7.21(br, 6H), 6.64(m, 1H),
10 6.47(m, 1H), 5.14(m, 2H), 4.21(m, 1H), 4.00(m, 2H), 3.68-3.58(br, 2H), 3.34(s, 3H), 2.34(m, 1H), 1.23-1.20(m, 4H)

ES-MS : 452(M+Na)

h) Synthesis of 1-ethyl-2-[2-[(S)-((S)-4-methoxy)pyrrolidin-2-yl]ethyl]-
15 indole-6-carbonitrile:

1.6g of the compound obtained in the above g) was treated
according to the same procedure as Example 1-k) to obtain 500mg of the
title compound as a brown oil.

20

¹H NMR(CDCl₃, ppm) : δ 7.58(m, 2H), 7.27(m, 1H), 6.30(s, 1H), 4.16(q,
2H, J=7.1Hz), 3.91(m, 1H), 3.28(s, 3H), 3.15(m, 2H), 2.92-2.78(m,
4H), 2.24(m, 1H), 2.02(m, 2H), 1.34(t, 3H, J=7.1Hz)

ES-MS : 298(M+1)⁺

25

i) Synthesis of tert-butyl (R)-2-[[[S)-2-[2-(6-cyano-1-ethylindol-2-yl)-
ethyl]-(S)-4-methoxypyrrolidinyl]carbonyl]pyrrolidine carboxylate:

450mg of the compound obtained in the above h) was treated
30 according to the same procedure as Example 11-a) to obtain 590mg of the
title compound as a pale brown oil.

¹H NMR(CDCl₃, ppm) : δ 7.55(m, 2H), 7.28(m, 1H), 6.39(m, 1H), 4.37(m,
1H), 4.16(m, 2H), 4.03(m, 1H), 3.62(m, 1H), 3.32(s, 3H), 2.82(m,
35 2H), 2.12-1.96(br, 4H), 1.85(m, 2H), 1.40(m, 9H), 1.33(m, 3H)

j) Synthesis of 1-ethyl-2-[2-[(S)-4-methoxy-1-[(R)-pyrrolidin-2-ylcarbonyl]pyrrolidin-(S)-2-yl]ethyl]indole-6-carbonitrile:

5 580mg of the compound obtained in the above i) was treated according to the same procedure as Example 1-l) to obtain 450mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.32(m, 1H), 6.42(s, 1H), 4.28(m, 1H), 4.15(m, 2H), 4.01(m, 1H), 3.75(m, 1H), 3.65(m, 1H), 3.33(s, 3H), 3.21(m, 1H), 2.80(m, 2H), 2.45(m, 1H), 2.10(m, 2H), 1.99-1.79(br, 7H), 1.36(m, 3H)

k) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]-(S)-4-methoxypyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

15 440mg of the compound obtained in the above j) and 0.19ml of ethyl 2-bromoacetate were treated according to the same procedure as Example 1-m) to obtain 380mg of the title compound as a pale yellow oil.

20 ES-MS : 481(M+1)⁺

l) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]-(S)-4-methoxypyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

25 360mg of the compound obtained in the above k) was treated according to the same procedure as Example 1-n) to obtain 90mg of the title compound as a pale yellow solid.

IR(KBr) : 3300, 3000, 1750, 1640 cm⁻¹

30 ES-MS : 498(M+1)⁺

Example 67 : Synthesis of ethyl-2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]propionate (Compound 109)

a) Synthesis of ethyl-2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]propionate:

300mg(0.823 mmole) of 1-ethyl-2-[2-[(S)-1-[(R)-pyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile was dissolved in 15 ml of acetonitrile, and 0.29ml(1.646 mmole) of diisopropylethylamine and 0.22ml(1.646 mmole) of ethyl 2-bromopropionate were added thereto. The reaction mixture was heated to 70°C, stirred for 4 hours, and then concentrated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 310mg of the title compound as a pale yellow oil.

ES-MS : 464 (M+1)⁺

¹H NMR(CDCl₃, ppm) : δ 7.61-7.56(m, 2H), 7.34-7.28(m, 1H), 6.46(s, 1H), 4.31(br, 1H), 4.21-4.14(m, 4H), 3.80-3.75(m, 1H), 3.61-3.53(m, 3H), 3.23-3.19(m, 1H), 2.86-2.81(m, 3H), 2.34-2.31(m, 1H), 2.01-1.77(m, 9H), 1.42-1.36(m, 3H), 1.32-1.22(m, 6H)

b) Synthesis of ethyl-2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]propionate:

310mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 220mg of the title compound as a pale yellow foam.

¹H NMR(MeOH-d₄, ppm) : δ 7.93-7.89(m, 1H), 7.64-7.58(m, 1H), 7.48-7.42(m, 1H), 6.46-6.42(m, 1H), 4.34-4.30(m, 3H), 4.18-4.14(m, 2H), 3.91-3.81(m, 1H), 3.65-3.61(m, 3H), 3.15-3.11(m, 1H), 2.88-2.81(m, 3H), 2.21-1.85(m, 10H), 1.42-1.27(m, 9H)

IR(KBr) : 3300, 2980, 1720, 1680, 1640, 1540 cm⁻¹

ES-MS : 482(M+1)⁺

Example 68 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate
(Compound 110)

a) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate:

100mg of the compound II-a obtained in Example 57-b) and 80 μ l
of ethyl 2-bromoacetate were reacted according to the same procedure as
Example 45-b) to obtain 88mg of the title compound.

¹H NMR(CDCl₃, ppm.) : δ 7.58(m, 2H), 7.27(m, 1H), 6.40(d, 1H), 4.38(m,
1H), 4.15(m, 4H), 3.69(m, 1H), 3.54(m, 2H), 3.30-3.10(m, 1H),
2.82(m, 3H), 2.30(m, 1H), 2.18-1.55(m, 12H), 1.42-1.17(m, 6H),
0.89(m, 3H)

b) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate:

88mg of the compound obtained in the above a) was treated
according to the same procedure as Example 1-n) to obtain 24mg of the
title compound.

¹H NMR(MeOH-d₄, ppm) : δ 8.00-6.24(m, 4H), 4.24(m, 5H), 3.64(m, 1H),
3.52(m, 2H), 3.41-3.10(m, 3H), 2.83(m, 5H), 2.31(m, 1H), 2.18-
1.54(m, 8H), 1.44-1.10(m, 6H), 0.84(m, 3H)

Example 69 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate (Compound 111)

a) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate:

135mg of the compound II-a obtained in Example 57-b) and 155 μ l
of ethyl 2-bromoacetate were reacted according to the same procedure as
Example 45-b) to obtain 112mg of the title compound.

¹H NMR(CDCl₃, ppm.) : δ 7.58(m, 2H), 7.28(d, 1H), 6.45(d, 1H, J=

8.20Hz), 4.30-4.00(m, 6H), 3.71-3.31(m, 3H), 3.25-3.05(m, 1H), 2.82(m, 3H), 2.45-2.20(m, 1H), 2.13-1.55(m, 11H), 1.38-1.12(m, 10H), 0.85(t, 2H), 0.75(t, 1H)

- 5 b) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate:

112mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 73mg of the
10 title compound.

¹H NMR(MeOH-d₄, ppm) : δ 7.82(s, 1H), 7.62(d, 1H, J=11.71Hz), 7.34(d, 1H, J=7.80Hz), 6.46(d, 1H, J=11.14Hz), 4.40-4.05(m, 6H), 3.75-3.40(m, 3H), 3.30-3.05(m, 1H), 2.99-2.66(m, 3H), 2.50-2.30(m, 1H), 2.13-1.52(m, 11H), 1.50-1.10(m, 10H), 0.90-0.70(m, 3H)

ES-MS : 524(M+1)⁺

20 Example 70 : Synthesis of ethyl-2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-phenylacetate (Compound 112)

- a) Synthesis of ethyl-2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-phenylacetate:

300mg of the compound II-a obtained in Example 57-b) and 300mg of ethyl 2-bromophenyl acetate were reacted according to the same procedure as Example 45-b) to obtain 300mg of the title compound as a pale yellow foam.

¹H NMR(CDCl₃, ppm) : δ 7.63-7.57(m, 2H), 7.51-7.48(m, 2H), 7.34-7.29(m, 4H), 6.43(s, 1H), 4.65(s, 1H), 4.24-4.19(m, 3H), 4.11-4.04(m, 3H), 3.45-3.41(m, 2H), 3.06-3.03(m, 1H), 2.84-2.71(m, 3H), 2.30-2.20(m, 2H), 1.98-1.82(m, 8H), 1.42(t, J=7.20Hz, 3H), 1.08(t, J=7.10Hz, 3H)

ES-MS : 526(M+1)⁺

b) Synthesis of ethyl-2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-phenylacetate:

130mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 80mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 8.04-7.95(m, 1H), 7.78-7.67(m, 1H), 7.50-7.45(m, 2H), 7.31-7.24(m, 4H), 6.51(m, 1H), 4.52(m, 1H), 4.37-4.34(m, 2H), 4.09-4.04(m, 3H), 3.49-3.44(m, 1H), 3.20-3.09(m, 2H), 2.98-2.65(m, 4H), 2.20-1.75(m, 10H), 1.47-1.42(m, 3H), 1.13-1.06(m, 3H)

ES-MS : 544(M+1)⁺

Example 71 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]-pyrrolidinyl]-2-(3-bromo-4-methoxyphenyl)acetate (Compound 113)

a) Synthesis of ethyl-2-bromo-2-(3-bromo-4-methoxyphenyl)acetate:

4.3g(0.0259 mole) of 4-methoxyphenylacetic acid was dissolved in 10ml of thionyl chloride, and the resulting solution was stirred for 18 hours at 70°C and then cooled to room temperature. To the reaction solution was added 50ml of carbon tetrachloride and then added 5.54g (0.0331 mole) of N-bromosuccinimide and 5 drops of 48% aqueous HBr solution. The resulting mixture was stirred for 4 hours at refluxing temperature and filtered to remove the insoluble materials. 50ml of ethanol was added to the filtrate and the mixture was stirred for 30 minutes and then evaporated under reduced pressure to remove the solvent. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:9)] to obtain 1.5g of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.72(d, J=2.23Hz, 1H), 7.45(dd, 1H, J=2.22Hz, 8.50Hz), 6.93(d, 1H, J=8.50Hz), 5.28(s, 1H), 4.32-4.25(m, 2H), 3.93

(s, 3H), 1.32(t, 3H, J=7.00Hz)

- b) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-(3-bromo-4-methoxyphenyl)-acetate:

100mg of the compound II-a obtained in Example 57-b) and 80mg of the compound obtained in the above a) were reacted according to the same procedure as Example 1-m) to obtain 170mg of the title compound as a pale yellow foam.

¹H NMR(CDCl₃, ppm) : δ 7.69-7.57(m, 3H), 7.40-7.29(m, 2H), 6.82(m, 1H), 6.44(m, 1H), 4.60(m, 1H), 4.24-4.21(m, 3H), 4.09-3.98(m, 3H), 3.78(m, 3H), 3.41-3.37(m, 2H), 3.24-3.05(m, 2H), 2.81-2.75(m, 2H), 2.21-1.72(m, 10H), 1.45-1.39(m, 3H), 1.24-1.08(m, 3H)

- c) Synthesis of ethyl-2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-(3-bromo-4-methoxyphenyl)-acetate:

170mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 70mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.85-7.75(m, 1H), 7.57-7.42(m, 2H), 7.33-7.29(m, 2H), 6.96-6.78(m, 1H), 6.36-6.33(m, 1H), 4.52(s, 1H), 4.21-4.18(m, 3H), 4.04-3.86(m, 3H), 3.73(m, 3H), 3.22-3.02(m, 2H), 2.91-2.78(m, 2H), 2.65-2.60(m, 2H), 2.10-1.65(m, 10H), 1.33-1.25(m, 3H), 1.09-1.00(m, 3H)

ES-MS : 653(M+1)⁺

IR(KBr) : 3380, 3020, 1740, 1635, 1540 cm⁻¹

Example 72 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(carbamomethyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethylindole-6-carboxamide (Compound 114)

681mg of methyl 2-[(R)-2-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate was dissolved in 25ml of ethanol solution saturated with HCl gas. The resulting solution was allowed to stand for one day at room temperature and then concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vacuum pump. The dried product was dissolved in 25ml of ethanol solution saturated with NH₃ gas, and the resulting solution was allowed to stand for 3 days at room temperature and then concentrated. The residue was purified with column chromatography [eluent: ethyl acetate/ethanol(1:1)] on NH-DM1020 silica to obtain 553mg of the title compound as a colorless solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.79(s, 1H), 7.53(d, 1H, J=8.42Hz), 7.32(d, 1H, J=8.27Hz), 6.40(s, 1H), 4.18(m, 3H), 3.57(m, 1H), 3.46(m, 4H), 2.84(m, 2H), 2.51-1.7(m, 12H), 1.28(t, 3H)

ES-MS : 439(M+1)⁺

Example 73 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-[(N-cyclopropylcarbamoyl)methyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]-ethyl]indole-6-carboxamide (Compound 115)

250mg of the compound II-a obtained in Example 57-b) and 92mg of N-cyclopropyl-2-chloroethanamide were reacted under the same conditions as Example 42 to obtain 125mg of the pale yellow solid product, which was then treated according to the same procedure as Example 1-n) to obtain 93mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 8.13(d, 1H, J=3.75Hz), 7.88(s, 1H), 7.61-7.38(m, 2H), 6.40(s, 1H), 4.27-4.13(m, 3H), 3.56-3.08(m, 3H), 2.90(s, 2H), 2.82(t, 2H, J=6.91Hz), 2.72-2.65(m, 1H), 2.50-1.67(m, 12H), 1.35(t, 3H, J=7.20Hz), 0.88-0.50(m, 4H)

ES-MS : 479(M+1)⁺

Example 74 : Synthesis of ethyl (S)-2-[2-[(R)-2-[[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-

acetylaminolpropanoate (Compound 116)

250mg of the compound II-a obtained in Example 57-b) and 133mg of ethyl-(S)-2-(2-chloroacetylaminolpropanoate were reacted under the same conditions as Example 42 to obtain 260mg of the pale yellow solid product, which was then treated according to the same procedure as Example 1-n) to obtain 96mg of the title compound as a pale yellow solid.

ES-MS : 539(M+1)⁺

Example 75 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[R)-1-(1-carbamoyl-3-hydroxypropyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]-ethyl]indole-6-carboxamidine (Compound 117)

- a) Synthesis of 1-ethyl-2-[2-[(S)-1-[[R)-1-(2-oxo-3-oxolanyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

700mg of the compound II-a obtained in Example 57-b) and 500mg of α -bromo- γ -butyrolactone were reacted according to the same procedure as Example 45-b) to obtain 650mg of the title compound as a white foam.

¹H NMR(CDCl₃, ppm) : δ 7.58-7.53(m, 2H), 7.30-7.26(m, 1H), 6.46(s, 1H), 4.39-4.34(m, 1H), 4.26(br, 1H), 4.21-4.13(m, 3H), 3.86-3.63(m, 3H), 3.51-3.45(m, 1H), 3.30-3.22(m, 1H), 2.96-2.90(m, 1H), 2.83-2.79(m, 2H), 2.39-2.11(m, 4H), 2.03-1.96(m, 4H), 1.84-1.66(m, 4H), 1.35(t, J=7.30Hz, 3H)

ES-MS : 449(M+1)⁺

- b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[R)-1-(1-carbamoyl-3-hydroxypropyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

450mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 370mg of the

title compound as a white solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.85-7.79(m, 2H), 7.56-7.52(m, 1H), 6.41(m, 1H), 4.23-4.18(m, 2H), 4.13-4.10(m, 1H), 3.64-3.59(m, 1H), 3.50-3.31(m, 4H), 3.07-2.87(m, 1H), 2.81-2.76(m, 2H), 2.68-2.61(m, 1H), 2.24-2.08(m, 2H), 1.92-1.71(m, 10H), 1.30(t, J=7.05Hz, 3H)

ES-MS : 483(M+1)⁺

IR(KBr) : 3340, 3220, 2980, 1680, 1630, 1540 cm⁻¹

10 Example 76 : Synthesis of 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-hydroxybutanoic acid (Compound 118)

250mg of 1-ethyl-2-[2-[(S)-1-[(R)-1-(1-carbamoyl-3-hydroxypropyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide was treated according to the same procedure as Example 44 to obtain 180mg of the title compound as a white solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.80-7.74(m, 1H), 7.56-7.48(m, 1H), 7.32-7.26(m, 1H), 6.39-6.34(m, 1H), 4.31-4.03(m, 4H), 3.69-3.64(m, 1H), 3.56-3.29(m, 4H), 3.04-2.96(m, 1H), 2.78(br, 3H), 2.20(br, 1H), 2.01-1.56(m, 11H), 1.29-1.24(m, 3H)

ES-MS : 484(M+1)⁺

IR(KBr) : 3400, 3000, 1630, 1580 cm⁻¹

25 Example 77 : Synthesis of 1-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]ethane-1,2-dicarboxylic acid (Compound 123)

30 a) Synthesis of diethyl-2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butane-1,4-dioate:

230mg(0.525 mmole) of ethyl-2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate was dissolved in 15ml of tetrahydrofuran and then cooled to -78°C. 0.79ml of lithium

bis(trimethylsilyl)amide (1.0M solution in tetrahydrofuran) was added dropwise thereto, and the reaction mixture was stirred for 30 minutes. 0.09ml(0.787 mmole) of ethyl bromoacetate diluted with 5ml of tetrahydrofuran was added dropwise thereto, and the resulting mixture was stirred for one hour. After water was added, the reaction solution thereby obtained was extracted with dichloromethane. The organic layer was dried over sodium sulfate and evaporated under reduced pressure to remove the solvent. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(40:1)] to obtain 180mg (Yield : 63.9%) of the title compound as a pale yellow foam.

¹H NMR(CDCl₃, ppm) : δ 7.61-7.51(m, 2H), 7.27(dd, 1H, J=1.30Hz, 8.10Hz), 6.46(s, 1H), 4.33(br, 1H), 4.21-4.06(m, 6H), 3.95-3.91(m, 1H), 3.84-3.80(m, 1H), 3.67-3.63(m, 1H), 3.49-3.45(m, 1H), 3.17-3.11(m, 1H), 2.99-2.91(m, 1H), 2.82-2.74(m, 3H), 2.60-2.55(m, 1H), 2.38-2.31(m, 1H), 2.02-1.95(m, 5H), 1.81-1.74(m, 4H), 1.38-1.17(m, 9H)

ES-MS : 537(M+1)⁺

b) Synthesis of 1-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidiny]carbonyl]pyrrolidiny]ethane-1,2-dicarboxylic acid:

400mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 180mg of diethyl 2-[(2)-2-[(2)-2-[2-(6-amidino-1-ethylindole-2-yl)ethyl]pyrrolidiny]carbonyl]pyrrolidiny]butane-1,4-dioate, which was then treated according to the same procedure as Example 44 to obtain 120mg of the title compound as white solid.

¹H NMR(MeOH-d₄) : δ 7.79(s, 1H), 7.51-7.47(m, 1H), 7.32-7.29(m, 1H), 6.42(s, 1H), 4.57(br, 1H), 4.23-4.19(m, 2H), 3.70(br, 2H), 3.52-3.48(m, 2H), 2.86-2.74(m, 4H), 2.60-2.54(m, 2H), 2.36-2.31(m, 1H), 2.12-2.09(m, 2H), 2.02-1.92(m, 6H), 1.66-1.61(m, 1H), 1.33-1.28(m, 3H)

ES-MS : 498(M+1)⁺

IR(KBr) : 3400, 3000, 1630, 1580 cm^{-1}

Example 78 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(2-oxo-3-oxolanyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 125)

130mg(0.269 mmole) of 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-hydroxybutanoic acid was dissolved in 5ml of 3N-HCl, and the resulting solution was stirred for 18 hours at room temperature and then evaporated under reduced pressure to remove the solvent. The residue was purified with column chromatography [eluent: ethyl acetate/methanol(3:1) on NH-DM1020 silica to obtain 70mg of the title compound as a white solid.

^1H NMR(MeOH- d_4 , ppm) : δ 7.79(s, 1H), 7.54-7.51(m, 1H), 7.34-7.30(m, 1H), 6.39(s, 1H), 4.31-4.20(m, 3H), 4.11-4.07(m, 2H), 3.68-3.64(m, 1H), 3.58-3.46(m, 4H), 2.80-2.75(m, 2H), 2.67-2.61(m, 1H), 2.30-2.12(m, 3H), 1.93-1.87(m, 4H), 1.80-1.73(m, 5H), 1.31-1.27(m, 3H)

ES-MS : 466(M+1) $^+$

IR(KBr) : 3400, 3020, 1770, 1640, 1540 cm^{-1}

Example 79 : Synthesis of ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate (Compound 126)

a) Synthesis of ethyl 4-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate:

400mg of the compound II-a obtained in Example 57-b) and 0.173 ml of ethyl 4-bromobutanoate were reacted according to the same procedure as Example 45-b) to obtain 453mg of the title compound as a viscous oil.

^1H NMR(CDCl_3 , ppm) : δ 7.59-7.53(m, 2H), 7.29(m, 1H), 6.47(s, 1H),

4.32-4.11(m, 3H), 4.05-3.99(m, 2H), 3.61(m, 2H), 3.27-3.18(m, 2H), 2.77(m, 2H), 2.66-1.62(m, 16H), 1.36(t, 3H, J=7.18Hz), 1.17(t, 3H, J=7.14Hz)

- 5 b) Synthesis of ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate :

453mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 228mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.79(s, 1H), 7.56-7.31(m, 2H), 6.40(s, 1H), 4.21(m, 2H), 4.10(brs, 1H), 3.91-3.80(m, 2H), 3.63-3.47(m, 2H), 3.08(m, 1H), 2.77(m, 2H), 2.52-1.65(m, 18H), 1.30(t, 3H, J=7.17 Hz), 1.08-0.97(m, 3H)

IR(KBr) : 3300, 3000, 1740, 1640, 1540, 1480 cm⁻¹

ES-MS : 496(M+1)⁺

20 Example 80 : Synthesis of 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoic acid (Compound 127)

122mg of ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]butanoate was treated according to the same procedure as Example 44 to obtain 89mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.79(s, 1H), 7.59-7.28(m, 2H), 6.38(s, 1H), 4.23-4.07(m, 3H), 3.62-3.50(m, 3H), 3.11(m, 1H), 2.77(m, 2H), 2.57-1.61(m, 18H), 1.28(t, 3H, J=7.14Hz)

IR(KBr) : 3400, 3000, 1700, 1640, 1540, 1480 cm⁻¹

ES-MS : 468(M+1)⁺

35 Example 81 : Synthesis of ethyl 5-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]pentanoate

(Compound 128)

a) Synthesis of ethyl 5-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]pentanoate:

5

138mg of the compound II-a obtained in Example 57-b) and 0.066 ml of ethyl 5-bromovalerate were reacted according to the same procedure as Example 45-b) to obtain 150mg of the title compound as a brown oil.

10

¹H NMR(CDCl₃, ppm) : δ 7.62-7.54(m, 2H), 6.46(s, 1H), 4.30-4.04(m, 5H), 3.68-3.51(m, 2H), 3.27-3.16(m, 2H), 2.80(t, 2H, J=7.91Hz), 2.69-1.59(m, 19H), 1.36(t, 3H, J=7.20Hz), 1.20(t, 3H, J=7.13Hz)

15

b) Synthesis of ethyl 5-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]pentanoate:

20

246mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 48mg of the title compound as a pale yellow solid.

25

¹H NMR(MeOH-d₄, ppm) : δ 7.78(s, 2H), 7.54-7.30(m, 2H), 6.37(s, 1H), 4.22-3.91(m, 5H), 3.60-3.47(m, 2H), 3.19-3.05(m, 2H), 2.81-2.73(m, 2H), 2.52-1.37(m, 19H), 1.30(t, 3H, J=7.15Hz), 1.05(t, 3H, J=7.88Hz)

30

IR(KBr) : 3100, 2990, 1740, 1670, 1630, 1530, 1470 cm⁻¹

ES-MS : 510(M+1)⁺

30

Example 82 : Synthesis of 5-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]pentanoic acid (Compound 129)

35

38mg of ethyl 5-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]pentanoate was treated according to the same procedure as Example 44 to obtain 16mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.80(s, 1H), 7.54-7.29(m, 2H), 6.36(s, 1H),
4.27-4.10(m, 3H), 3.65-3.42(m, 2H), 3.19-3.03(m, 2H), 2.82-2.71
(m, 2H), 2.57-1.41(m, 19H), 1.29(t, 3H, J=7.19Hz)

ES-MS : 482(M+1)⁺

5

Example 83 : Synthesis of ethyl 6-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate (Compound 130)

- 10 a) Synthesis of ethyl 6-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate:

15 160mg of the compound II-a obtained in Example 57-b) and 0.086 ml of ethyl 6-bromohexanoate were reacted according to the same procedure as Example 45-b) to obtain 168mg of the title compound as a brown oil.

20 ¹H NMR(CDCl₃, ppm) : δ 7.61-7.54(m, 2H), 7.30(m, 1H), 6.45(s, 1H), 4.27(brs, 1H), 4.18-4.04(m, 4H), 3.68-3.52(m, 2H), 3.26-3.17(m, 2H), 2.80(t, 2H, J=7.95Hz), 2.23(t, 2H, J=7.45Hz), 2.66-1.25(m, 19H), 1.36(t, 3H, J=7.18Hz), 1.21(t, 3H, J=7.13Hz)

- b) Synthesis of ethyl 6-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate:

25

161mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 41mg of the title compound as a pale yellow solid.

30 ¹H NMR(MeOH-d₄, ppm) : δ 7.78(s, 2H), 7.54-7.30(m, 2H), 6.36(s, 1H), 4.26-3.88(m, 5H), 3.61-3.46(m, 2H), 3.19-3.03(m, 2H), 2.81-2.72(m, 2H), 2.52-1.38(m, 2H), 1.18(t, 3H, J=7.18Hz), 1.06(t, 3H, J=7.12Hz)

IR(KBr) : 3200, 2970, 1730, 1630, 1530, 1470, 1340 cm⁻¹

35 ES-MS : 524(M+1)⁺

Example 84 : Synthesis of 6-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethylpyrrolidinyl]carbonyl]pyrrolidinyl]hexanoic acid (Compound 131)

5 30mg of ethyl 6-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethylpyrrolidinyl]carbonyl]pyrrolidinyl]hexanoate was treated according to the same procedure as Example 44 to obtain 26mg of the title compound as a pale yellow solid.

10 ¹H NMR(MeOH-d₄, ppm) : δ 7.80(s, 1H), 7.54-7.29(m, 2H), 6.34(s, 1H), 4.27-4.11(m, 3H), 3.66-3.45(m, 2H), 3.18-3.04(m, 2H), 2.82-2.71(m, 2H), 2.50-1.17(m, 21H), 1.28(t, 3H, J=7.15Hz)

ES-MS : 496(M+1)⁺

15 **Example 85 : Synthesis of ethyl 2-[(R,R)-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethylpyrrolidinyl]carbonyl]-4-methoxypyrrolidinyl]acetate (Compound 135)**

20 a) Synthesis of methyl (R,R)-4-methoxy-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylate:

500mg of 4-cis-hydroxy-D-proline was dissolved in 4ml of methanol, and 0.4ml of acetyl chloride was added dropwise at 0°C. 0.14 ml of thionyl chloride was added dropwise at room temperature, and the
25 resulting mixture was heated under refluxing for 2 hours with stirring. The reaction solution was cooled to room temperature and then evaporated under reduced pressure to obtain 704mg of the white solid product, which was then dissolved in 10ml of dichloromethane. To the
30 resulting solution was added dropwise 1.07ml of triethylamine at 0°C and then added 930mg of (BOC)₂O. The reaction mixture was stirred for 2.5 hours at room temperature, diluted with 150ml of dichloromethane, washed with 30ml of 2N-HCl solution and 30ml of water, dried over sodium sulfate and then filtered. The filtrate was then evaporated under
35 reduced pressure to obtain 780mg of the brown solid, which was dissolved in 15ml of anhydrous tetrahydrofuran. To the resulting solution was

then added 138mg of NaH, and the mixture was stirred for one hour at room temperature. 0.214ml of methyl iodide was slowly added dropwise thereto, and the reaction mixture was heated under refluxing overnight with stirring. After 1ml of water was added dropwise, the reaction solution was evaporated under reduced pressure to obtain the residue, which was then diluted with 150ml of dichloromethane, washed with 50ml of water, dried over sodium sulfate and then filtered. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 404mg of the title compound as a viscous oil.

¹H NMR(CDCl₃, ppm) : δ 4.46-4.28(m, 1H), 3.94(brs, 1H), 3.73(s, 3H), 3.63-3.49(m, 2H), 3.30(d, 3H, J=9.48Hz), 2.41-2.22(m, 1H), 2.11-1.98(m, 1H), 1.44(m, 9H)

b) Synthesis of (R,R)-4-methoxy-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid:

520mg of the compound obtained in the above a) was reacted in the presence of methanol solvent under the same conditions as Example 44 to obtain 480mg of the title compound as a colorless oil.

¹H NMR(CDCl₃, ppm) : δ 4.47-4.34(m, 1H), 3.97(brs, 1H), 3.64-3.49(m, 2H), 3.33(s, 3H), 2.44-2.10(m, 2H), 1.49-1.42(m, 9H)

c) Synthesis of tert-butyl (R,R)-2-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]-4-methoxypyrrolidine carboxylate:

203mg of the compound I-a obtained in Example 1-1) was reacted with the compound obtained in the above b) according to the same procedure as Example 11-a) to obtain 212mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.58-7.52(m, 2H), 7.30(m, 1H), 6.39(m, 1H), 4.31(m, 1H), 4.21-4.10(m, 2H), 3.97-3.40(m, 6H), 3.32(s, 3H), 2.88-

2.76(m, 2H), 2.58-1.67(m, 8H), 1.45-1.40(m, 9H), 1.35(t, 3H, J=7.11Hz)

- 5 d) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R,R)-4-methoxypyrrolidin-2-yl]-carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

210mg of the compound obtained in the above c) was treated according to the same procedure as Example 1-l) to obtain 145mg of the title compound as a pale yellow solid.

10

¹H NMR(CDCl₃, ppm) : δ 7.59-7.54(m, 2H), 7.29(m, 1H), 6.40(s, 1H), 4.28 (brs, 1H), 4.18-4.10(m, 2H), 4.04-3.93(m, 2H), 3.67-3.42(m, 2H), 3.31(s, 3H), 3.21(s, 1H), 3.00-2.92(m, 1H), 2.85-2.74(m, 2H), 2.43-1.72(m, 9H), 1.36(t, 3H, J=7.19Hz)

15

- e) Synthesis of ethyl 2-[(R,R)-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]-4-methoxypyrrolidin-2-yl]acetate:

98mg of the compound obtained in the above d) was reacted with 30μl of ethyl 2-bromoacetate according to the same procedure as Example 1-m) to obtain 93mg of the title compound as a yellow oil.

20 ¹H NMR(CDCl₃, ppm) : δ 7.58-7.53(m, 2H), 7.29(m, 1H), 6.42(s, 1H), 4.31 (brs, 1H), 4.20-4.11(m, 4H), 4.08-4.01(m, 2H), 3.62-3.50(m, 5H), 3.29(s, 3H), 2.82-2.73(m, 3H), 2.35-1.59(m, 8H), 1.35(t, 3H, J=7.24Hz), 1.26(t, 3H, J=7.13Hz)

25

- f) Synthesis of ethyl 2-[(R,R)-[[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]-4-methoxypyrrolidin-2-yl]acetate:

30

93mg of the compound obtained in the above e) was treated according to the same procedure as Example 1-n) to obtain 16mg of the title compound as a pale yellow solid.

35 ¹H NMR(MeOH-d₄, ppm) : δ 7.83(s, 1H), 7.54-7.31(m, 2H), 6.38(s, 1H), 4.21-3.85(m, 7H), 3.58-3.29(m, 5H), 3.18(s, 3H), 2.82-2.73(m,

2H), 2.61(m, 1H), 2.19-1.66(m, 8H), 1.29(t, 3H, J=6.85Hz), 1.17-1.08(m, 3H)

ES-MS : 498(M+1)⁺

5 **Example 86 : Synthesis of ethyl-2-[(R,R)-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]piperidinyl]carbonyl]-4-methoxypyrrolidin-2-yl]acetate (Compound 136)**

10 a) Synthesis of (R,R)-4-hydroxy-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid:

0.81g of (R,R)-4-hydroxypyrrolidine-2-carboxylic acid was treated according to the same procedure as Example 66-a) to obtain 1g of the title compound as a colorless oil.

15 ¹H NMR(CDCl₃, ppm) : δ 7.31(m, 5H), 5.19(m, 2H), 4.53(m, 1H), 4.43(m, 1H), 3.60(m, 2H), 2.24(m, 2H)

20 b) Synthesis of (R,R)-4-methoxy-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid:

1g of the compound obtained in the above a) was treated according to the same procedure as Example 66-d) to obtain 1.1g of the title compound as a pale brown oil.

25 ¹H NMR(CDCl₃, ppm) : δ 7.31(m, 5H), 5.16(m, 2H), 4.45(m, 1H), 3.95(m, 1H), 3.64(m, 2H), 3.26(s, 3H), 2.45-2.38(m, 1H), 2.24(m, 1H)

30 c) Synthesis of phenylmethyl-2-(R,R)-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]piperidinyl]carbonyl]-4-methoxypyrrolidine carboxylate:

0.92g of 1-ethyl-2-[2-((S)-2-piperidyl)ethyl]indole-6-carbonitrile and 1.1g of (R,R)-4-methoxy-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid were treated according to the same procedure as Example 35 11-a) to obtain 500mg of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.35(m, 5H), 7.27(m, 1H), 6.33(s, 1H), 5.09(m, 2H), 4.16(m, 1H), 3.95(m, 2H), 3.66(m, 2H), 3.26(m, 3H), 2.32(m, 2H), 1.41(m, 2H), 1.25(m, 3H)

- 5 d) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R,R)-4-methoxypyrrolidin-2-yl)-carbonyl]piperidin-2-yl]ethyl]indole-6-carbonitrile:

480mg of the compound obtained in the above c) was treated according to the same procedure as Example 1-k) to obtain 270mg of the
10 title compound as a pale yellow solid.

- e) Synthesis of ethyl 2-[(R,R)-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]piperidiny]carbonyl]-4-methoxypyrrolidin-2-yl]acetate:

15 250mg of the compound obtained in the above d) and 0.1ml of ethyl 2-bromoacetate were treated according to the same procedure as Example 1-m) to obtain 200mg of the title compound as a pale yellow oil.

20 ¹H NMR(CDCl₃, ppm) : δ 7.78(m, 1H), 7.54(m, 1H), 7.33(m, 1H), 6.31(s, 1H), 4.95(br, 1H), 4.12(m, 4H), 3.97(m, 2H), 3.72-3.60(m, 2H), 3.28(m, 3H), 3.02(m, 1H), 2.71(m, 1H), 2.61-2.49(m, 2H), 2.19(m, 1H), 1.30(m, 3H), 1.26-1.19(m, 6H)

- 25 f) Synthesis of ethyl 2-[(R,R)-[[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]piperidiny]carbonyl]-4-methoxypyrrolidin-2-yl]acetate:

190mg of the compound obtained in the above e) was treated according to the same procedure as Example 1-n) to obtain 50mg of the
30 title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.77(m, 1H), 7.54(m, 1H), 7.33(m, 1H), 6.31(s, 1H), 4.95(br, 1H), 4.15(m, 4H), 3.98-3.87(m, 2H), 3.62(m, 2H), 3.28(m, 3H), 3.05(m, 1H), 2.70(m, 1H), 2.77-2.52(m, 2H), 2.18(br, 1H), 1.84(m, 2H), 1.67(m, 5H), 1.32(m, 3H), 1.24(m, 3H)

35 IR(KBr) : 3400, 2920, 1720, 1630, 1460 cm⁻¹

ES-MS : 512(M+1)⁺

Example 87 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(2-hydroxyethyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 140)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(2-hydroxyethyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

130mg of the compound II-a obtained in Example 57-b) and 0.1ml of 2-bromoethanol were treated according to the same procedure as Example 45-b) to obtain 140mg of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : 7.50(m, 2H), 7.25(s, 1H), 6.34(s, 1H), 4.20(m, 1H), 4.10(t, 3H), 3.52(m, 2H), 3.37(m, 2H), 3.21(m, 2H), 2.76(m, 2H), 2.44(m, 2H), 2.32-1.60(m, 11H), 1.27(t, 3H)

ES-MS : 409(M+1)⁺

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(2-hydroxyethyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

140mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 45mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.80(s, 1H), 7.58(m, 1H), 7.34(s, 1H), 6.83(d, 1H), 4.20(m, 1H), 4.05(s, 3H), 3.57(m, 2H), 3.60(m, 2H), 3.47(m, 2H), 3.20(m, 2H), 2.83(m, 2H), 2.65(m, 2H), 2.40-1.80(m, 11H), 1.37(m, 3H)

ES-MS : 426(M+1)⁺

Example 88 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-[2-(methylamino)acetyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamide (Compound 142)

- a) Synthesis of N-[2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-oxoethyl]-N-methyl-(tert-butoxy)formamide:

101mg of the compound II-a obtained in Example 57-b) and 52mg of N-(tert-butoxycarbonyl)sarcosine were reacted according to the same procedure as Example 11-a) to obtain 106mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.61-7.52(m, 2H), 7.27(m, 1H), 6.34(s, 1H), 4.67(m, 1H), 4.28-4.12(m, 3H), 3.81-3.44(m, 6H), 2.88(s, 3H), 2.79(t, 2H, J=7.90Hz), 2.28-1.73(m, 10H), 1.44(s, 9H), 1.35(t, 3H, J=7.31Hz)

- b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-[2-(methylamino)acetyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

103mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 46mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.81(s, 1H), 7.55-7.31(m, 2H), 6.37(s, 1H), 4.57(m, 1H), 4.22-4.08(m, 3H), 3.75-3.47(m, 4H), 3.31(s, 2H), 2.77(brs, 2H), 2.27(s, 3H), 2.19-1.77(m, 10H), 1.29(t, 3H, J=7.12Hz)

IR(KBr) : 3440, 1640, 1025 cm⁻¹

ES-MS : 453(M+1)⁺

Example 89 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-[(S)-2-aminopropanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 143)

- a) Synthesis of N-[(1S)-2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-1-methyl-2-oxoethyl]-(tert-butoxy)formamide:

300mg of the compound II-a obtained in Example 57-b) and 187mg of (S)-2-[(tert-butoxy)carbonylamino]propanoic acid were reacted according to the same procedure as Example 11-a) to obtain 210mg of the title compound as a pale yellow solid.

5

^1H NMR(CDCl_3 , ppm) : δ 7.55(m, 2H), 7.24(m, 1H), 6.35(s, 1H), 4.57(m, 1H), 4.49(m, 1H), 4.32(m, 1H), 4.13(m, 2H), 3.79(m, 2H), 3.58-3.43(br, 2H), 2.81(m, 2H), 2.12(m, 4H), 1.42(m, 9H), 1.35(m, 6H)
ES-MS : 356(M+1) $^+$

10

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-((S)-2-aminopropanoyl)-pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

200mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 100mg of the title compound as a yellowish white solid.

^1H NMR(CDCl_3 , ppm) : δ 7.80(m, 1H), 7.38(m, 1H), 7.23(m, 1H), 6.15(m, 1H), 4.57(m, 2H), 4.13(br, 3H), 3.83(m, 2H), 3.66(m, 1H), 3.45(m, 2H), 2.71(m, 2H), 2.12(m, 3H), 1.97-1.84(br, 6H), 1.25-1.17(m, 6H)

20

IR(KBr) : 3420, 3000, 1640 cm^{-1}

ES-MS : 453(M+1) $^+$

25

Example 90 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(2-amino-butanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 144)

a) Synthesis of N-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]-1-ethyl-2-oxoethyl](tert-butoxy)formamide:

30

400mg of the compound II-a obtained in Example 57-b) and 270mg of 3-[(tert-butoxy)carbonylamino]butanoic acid were reacted according to the same procedure as Example 11-a) to obtain 350mg of the title

35

compound as a yellow oil.

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-(2-aminobutanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

5

340mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 190mg of the title compound as a yellowish white solid.

¹H NMR(CDCl₃, ppm) : δ 7.83(m, 1H), 7.32(m, 1H), 7.16(m, 1H), 6.21(s, 1H), 4.60(m, 2H), 4.18(m, 5H), 3.88(m, 2H), 3.78(m, 2H), 3.64(m, 1H), 3.48(m, 5H), 2.72(m, 3H), 2.16(m, 5H), 1.24(m, 5H), 0.95(m, 3H)

IR(KBr) : 3400, 3000, 1640 cm⁻¹

ES-MS : 467(M+1)⁺

15

Example 91 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-((S)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl]cabonyl]pyrrolidin-2-yl]-ethyl]indole-6-carboxamidine (Compound 145)

20

a) Synthesis of N-[(1S)-2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-1-isopropyl-2-oxo-ethyl](tert-butoxy)formamide:

25 250mg of the compound II-a obtained in Example 57-b) and 298mg of 3-methyl-(S)-2-[(tert-butoxy)carbonylamino]butanoic acid were reacted according to the same procedure as Example 11-a) to obtain 300mg of the title compound as a yellowish white solid.

30 ¹H NMR(CDCl₃, ppm) : δ 7.52(m, 2H), 7.30(m, 1H), 6.32(s, 1H), 5.18(m, 1H), 4.54(m, 1H), 4.23-4.14(m, 1H), 4.15(q, 2H), 3.88(m, 2H), 3.68-3.39(m, 2H) 2.82(m, 2H), 2.71-2.32(m, 10H), 1.38(brs, 9H), 1.34(t, 3H), 0.98(m, 3H), 0.85(m, 4H)

35 b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-((S)-2-amino-3-methylbuta-

noyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-1-ethylindole-6-carboxamidine:

140mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 59mg of the title compound as a pale yellowish white solid.

¹H NMR(CDCl₃, ppm) : δ 7.69(m, 1H), 7.42(m, 1H), 7.22(m, 1H), 6.28(s, 1H), 4.58(m, 1H), 4.33-4.16(m, 2H), 4.11(q, 2H), 3.91-3.72(m, 2H), 3.58-3.38(m, 2H), 2.73(m, 2H), 2.22-1.77(m, 10H), 1.28(t, 3H), 0.89(m, 7H)

ES-MS : 482(M+2)⁺

IR(KBr) : 2997, 1642, 1543, 1480 cm⁻¹

Example 92 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-[(S)-2-(methanesulfonylamino)propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 146)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-((S)-2-aminopropanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

294mg of N-[(S)-2-[(R)-2-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-1-methyl-2-oxoethyl](tert-butoxy)formamide was treated according to the same procedure as Example 1-l) to obtain 220mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.21(m, 1H), 6.37(s, 1H), 4.58(m, 1H), 4.27(m, 1H), 4.14(q, 2H), 3.82-3.58(m, 3H), 3.42(m, 2H), 2.82(m, 2H), 2.26-1.78(m, 10H), 1.37(t, 3H), 1.21(t, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-[(S)-2-(methanesulfonylamino)propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

140mg of the compound obtained in the above a) and 20μl of

methanesulfonyl chloride were reacted according to the same procedure as Example 1-m) to obtain 120mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.59(m, 2H), 7.28(m, 1H), 6.41(s, 1H), 5.13(m, 1H), 4.61(m, 1H), 4.32(m, 1H), 4.14(q, 2H), 3.89-3.75(m, 2H), 3.55-3.48(m, 2H), 2.86(s, 6H), 2.75(m, 2H), 2.28-1.74(m, 10H), 1.38(m, 6H)

ES-MS : 514(M+1)⁺

10

c) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-[(S)-2-(methanesulfonylamino)propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

15 120mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 61mg of the title compound as a pale yellowish white solid.

¹H NMR(CDCl₃, ppm) : δ 7.94(m, 1H), 7.41(m, 1H), 7.23(m, 1H), 6.22(s, 1H), 4.61(m, 1H), 4.35(m, 1H), 4.18(m, 3H), 3.92-3.75(m, 2H), 3.56-3.38(m, 2H), 2.86(s, 3H), 2.68(m, 2H), 2.22-1.71(m, 10H), 1.42(t, 3H), 1.24(m, 3H)

ES-MS : 531(M+1)⁺

IR(KBr) : 2998, 1643, 1541, 1342 cm⁻¹

25

Example 93 : Synthesis of ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-3-amino-4-oxobutanoate (Compound 147)

30 a) Synthesis of phenylmethyl-4-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-3-[(tert-butoxy)carbonylamino]-4-oxobutanoate:

35 0.6g of the compound II-a obtained in Example 57-b) and 798mg of (S)-2-[(tert-butoxy)carbonylamino]-3-(benzyloxycarbonyl)propanoic

acid were reacted according to the same procedure as Example 11-a) to obtain 1.1g of the title compound as a yellowish white solid.

¹H NMR(CDCl₃, ppm) : δ 7.52(m, 2H), 7.35-7.17(m, 6H), 6.33(s, 1H), 5.26
5 (m, 1H), 4.98(m, 2H), 4.88(m, 1H), 4.47(m, 1H), 4.12(q, 2H), 3.78-
3.39(m, 4H), 2.88-2.66(m, 4H), 2.23-1.71(m, 10H), 1.39(brs, 9H),
1.29(t, 3H)

ES-MS : 682(M+Na⁺), 670(M+1)⁺

- 10 b) Synthesis of ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-
ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-3-amino-4-oxobutanoate:

1.1g of the compound obtained in the above a) was treated
according to the same procedure as Example 1-n) to obtain 250mg of the
15 title compound as a yellowish white solid.

¹H NMR(CDCl₃, ppm) : δ 7.75(m, 1H), 7.39(m, 1H), 7.22(m, 1H), 6.27(s,
1H), 4.66-4.47(m, 1H), 4.27-3.95(m, 6H), 3.86-3.37(m, 4H), 2.79-
2.42(m, 4H), 2.19-1.73(m, 10H), 1.31-1.19(m, 6H)

20 ES-MS : 525(M+1)⁺

IR(KBr) : 3028, 1768, 1647, 1374 cm⁻¹

Example 94 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-((S)-2-
25 amino-3-carbamoylpropanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-
yl]ethyl]indole-6-carboxamide (Compound 148)

1.1g of phenylmethyl-4-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-
2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-3-[(tert-butoxy)carbonyl-
amino]-4-oxobutanoate was treated according to the same procedure as
30 Example 1-n) to obtain 150mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.77(m, 1H), 7.48(m, 1H), 7.32(m, 1H), 6.34(s,
1H), 4.49(m, 1H), 4.22-4.07(m, 3H), 3.92(m, 1H), 3.66(m, 2H),
3.38(m, 2H), 2.71(m, 2H), 2.50-2.25(m, 2H), 2.22-1.74(m, 10H),
35 1.30(t, 3H)

ES-MS : 496(M+1)⁺

IR : 3086, 1637, 1367 cm⁻¹

5 Example 95 : Synthesis of 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-3-amino-4-oxobutanoic acid (Compound 149)

150mg of ethyl-4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(3S)-3-amino-4-oxobutanoate
 10 and 50mg of 2-[2-[(S)-1-[(R)-1-[(S)-2-amino-3-carbamoyl]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-1-ethylindole-6-carboxamide were reacted under the same conditions as Example 44 to obtain 145mg of the title compound as a white solid.

15 ¹H NMR(MeOH-d₄, ppm) : δ 7.75(m, 1H), 7.51(m, 1H), 7.30(m, 1H), 6.32(s, 1H), 4.56-4.28(m, 1H), 4.21-4.08(m, 3H), 3.93(m, 1H), 3.81-3.66(m, 2H), 3.52-3.25(m, 2H), 2.76(m, 2H), 2.54-2.18(m, 2H), 2.12-1.69(m, 10H), 1.28(t, 3H)

ES-MS : 498(M+2)⁺

20 IR(KBr) : 1632, 1372 cm⁻¹

25 Example 96 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-amino-propanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 155)

a) Synthesis of 2-[2-[(S)-1-[(R)-1-(3-chloropropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-1-ethylindole-6-carbonitrile:

800mg of the compound II-a obtained in Example 57-b) and 0.475 ml of 3-chloropropionic acid were reacted according to the same procedure as Example 11-a) to obtain 926mg of the title compound.

35 ¹H NMR(CDCl₃, ppm) : δ 7.61(s, 1H), 7.56(d, 1H, J=8.81Hz), 7.26(d, 1H, J=8.98Hz), 6.37(s, 1H), 4.65(m, 1H), 4.28(m, 1H), 4.15(q, 2H), 3.82(m, 2H), 3.71(m, 4H), 3.62-3.40(m, 2H), 2.78(m, 4H), 2.30-1.78

(m, 10H), 1.33(t, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-aminopropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

5

320mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 98mg of the title compound as a pale yellow solid.

10 ¹H NMR(MeOH-d₄, ppm) : δ 7.92(s, 1H), 7.65(d, 1H, J=8.25Hz), 7.46(d, 1H), 6.49(s, 1H), 4.40-4.16(m, 3H), 3.87(m, 1H), 3.78-3.53(m, 4H), 2.91(m, 4H), 2.89(m, 2H), 2.40-1.80(m, 10H), 1.41(t, 3H)

15 Example 97 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-amino-2-methylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamide (Compound 156)

a) Synthesis of N-[3-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-2-methyl-3-oxopropyl](tert-butoxy)formamide:

20

430mg of the compound II-a obtained in Example 57-b) and 290mg of 2-methyl-3-[(tert-butoxy)carbonylamino]propanoic acid were reacted according to the same procedure as Example 11-a) to obtain 270mg of the title compound as a yellow oil.

25

¹H NMR(CDCl₃, ppm) : δ 7.57(m, 2H), 7.28(m, 1H), 6.36(d, 1H), 4.62(m, 1H), 4.26(m, 1H), 4.16(m, 2H), 3.47(m, 2H), 3.22(m, 2H), 2.79(m, 2H), 2.15(m, 3H), 1.93(m, 6H), 1.60(m, 9H), 1.27(m, 3H), 1.12(t, 3H)

30

ES-MS : 550(M+1)⁺, 573(M+Na)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-amino-2-methylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide

35

250mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 100mg of the title compound as a pale yellow solid.

- 5 ¹H NMR(CDCl₃, ppm) : δ 7.89(d, 1H, J=7.00Hz), 7.32(m, 1H), 7.18(m, 1H),
6.19(d, 1H, J=8.70Hz), 4.61(m, 1H), 4.14(m, 2H), 3.85(m, 3H),
3.45(m, 2H), 2.69(m, 2H), 2.19(m, 6H), 1.26(m, 5H), 1.07(m, 3H),
1.02(m, 3H)
IR(KBr) : 3420, 1650 cm⁻¹
10 ES-MS : 467(M+1)'

Example 98 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-amino-
butanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethylindole-6-
carboxamidine (Compound 157)

15

- a) Synthesis of N-[3-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-
-pyrrolidinyl]carbonyl]pyrrolidinyl]-1-methyl-3-oxopropyl](tert-butoxy)
formamide:

- 20 430mg of the compound II-a obtained in Example 57-b) and 290mg
of 3-[(tert-butoxy)carbonylamino]butanoic acid were reacted according to
the same procedure as Example 11-a) to obtain 260mg of the title
compound as a yellow oil.

- 25 ¹H NMR(CDCl₃, ppm) : δ 7.57(m, 2H), 7.29(m, 1H), 6.36(s, 1H), 4.62(m,
1H), 4.15(t, 2H, J=7.20Hz), 4.03(m, 1H), 3.69(m, 2H), 3.47(m, 3H),
2.80(m, 2H), 2.57(m, 2H), 2.16(m, 3H), 1.93(m, 6H), 1.43(m, 9H),
1.37(m, 3H), 1.20(m, 3H)
ES-MS : 550(M+1)'

30

- b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-aminobutanoyl)pyrrolidin-
2-yl]carbonyl]pyrrolidin-2-yl]ethylindole-6-carboxamidine:

- 250mg of the compound obtained in the above a) was treated
35 according to the same procedure as Example 1-n) to obtain 110mg of the

title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.87(m, 1H), 7.35(m, 1H), 7.20(m, 1H), 6.21(s, 1H), 4.60(m, 1H), 4.21(m, 4H), 3.85(m, 2H), 2.72(m, 3H), 2.11(br, 6H), 1.98(br, 3H), 1.21(m, 3H), 1.04(m, 3H)

IR(KBr) : 3400, 2840, 1650, 1020 cm⁻¹

ES-MS : 467(M+1)⁺

Example 99 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-[3-[(methanesulfonyl)amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 158)

a) Synthesis of N-[3-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]-3-oxopropyl](tert-butoxy)formamide

500mg of the compound II-a obtained in Example 57-b) and 290mg of 3-[(tert-butoxy)carbonylamino]propanoic acid were reacted according to the same procedure as Example 11-a) to obtain 340mg of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.55(m, 2H), 7.26(m, 1H), 6.37(s, 1H), 4.63(m, 1H), 4.28(m, 1H), 4.15(t, 2H, J=7.20Hz), 3.81(m, 1H), 3.66(m, 2H), 3.41(m, 6H), 2.80(m, 2H), 2.52(m, 2H), 2.18(m, 4H), 1.98(m, 6H), 1.42(m, 9H), 1.32(m, 3H)

ES-MS : 536(M+1)⁺, 558(M+Na), 574(M+K)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-(3-aminopropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

340mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-1) to obtain 160mg of the title compound as a yellow oil.

c) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-[3-[(methanesulfonyl)amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbo-

nitrile:

180mg of the compound obtained in the above b) and 55 μ l of
methanesulfonyl chloride were reacted according to the same procedure as
5 Example 1-m) to obtain 100mg of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.25(m, 1H), 6.41(s, 1H), 4.62(m,
1H), 4.24(m, 1H), 4.18(t, 2H, J=7.20Hz), 3.75(m, 2H), 3.48-3.39(m,
4H), 2.87-2.79(m, 4H), 2.20(m, 2H), 2.01-1.90(br, 7H), 1.35(m,
10 3H)

d) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-[3-[(methanesulfonyl)amino]
-propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-
carboxamide:

15

100mg of the compound obtained in the above c) was treated
according to the same procedure as Example 1-n) to obtain 60mg of the
title compound as a yellowish white solid.

20 ¹H NMR(CDCl₃, ppm) : δ 7.69(s, 1H), 7.54(m, 1H), 7.28(m, 1H), 6.34(s,
1H), 4.60(m, 1H), 4.21(m, 3H), 3.73(m, 2H), 3.34(m, 2H), 2.83(s,
3H), 2.79(m, 2H), 2.16(m, 4H), 2.02-1.96(br, 4H), 1.33(t, 3H,
J=7.10Hz)

IR(KBr) : 3300, 3000, 1640 cm⁻¹

25 ES-MS : 531(M+1)⁺

Example 100 : Synthesis of ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-
1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-2-
amino-4-oxobutanoate (Compound 159)

30

a) Synthesis of phenylmethyl-4-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-
2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-2-[(*tert*-butoxy)carbo-
nylamino]-4-oxobutanoate:

35

0.6g of the compound II-a obtained in Example 57-b) and 0.798g

of (S)-3-[(tert-butoxy)carbonylamino]-3-(benzyloxycarbonyl)propanoic acid were reacted according to the same procedure as Example 11-a) to obtain 1.08g of the title compound as a pale yellow solid.

5 ¹H NMR(CDCl₃, ppm) : δ 7.51(m, 1H), 7.49(m, 1H), 7.32-7.04(m, 6H), 6.30 (s, 1H), 5.67(m, 1H), 4.86-4.72(m, 2H), 4.59-4.46(m, 1H), 4.27-4.01(m, 3H), 3.83-3.58(m, 2H), 3.46-3.37(m, 2H), 3.09-2.66(m, 4H), 2.27-1.69(m, 10H), 1.42(brs, 9H), 1.25(t, 3H)
ES-MS : 692(M+Na⁺), 670(M+1)⁺

10

b) Synthesis of ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-2-amino-4-oxobutanoate:

1.08g of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 250mg of the title compound as a pale yellow solid.

15 ¹H NMR(CDCl₃, ppm) : δ 7.77(m, 1H), 7.44(m, 1H), 7.28(m, 1H), 6.28(s, 1H), 4.62(m, 1H), 4.21(m, 4H), 4.06(q, 2H), 3.90-3.71(m, 2H),
20 3.61-3.39(m, 2H), 2.71(m, 4H), 2.28-1.72(m, 10H), 1.32(t, 3H), 1.18(t, 3H)
ES-MS : 525(M+1)⁺
IR(KBr) : 1752, 1648, 1375 cm⁻¹

25 Example 101 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-((S)-3-amino-3-carbamoylpropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethylindole-6-carboxamide (Compound 160)

1.08g of phenylmethyl 4-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-[(tert-butoxy)carbo-
30 -nylamino]-4-oxobutanoate was treated according to the same procedure as Example 1-n) to obtain 230mg of the title compound as a white solid.

¹H NMR(MeOH-d₄) : δ 7.78(m, 1H), 7.49(m, 1H), 7.28(m, 1H), 6.35(s, 1H),
35 4.53(m, 1H), 4.19-4.08(m, 3H), 3.76-3.38(m, 5H), 2.81-2.42(m,

4H), 2.25-1.71(m, 10H), 1.28(t, 3H)

ES-MS : 496(M+1)⁺

IR(KBr) : 3098, 1641, 1498, 1365 cm⁻¹

5 Example 102 : Synthesis of 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-2-amino-4-oxobutanoic acid (Compound 161)

170mg of ethyl-4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-2-amino-4-oxobutanoate
 10 and 130mg of 1-ethyl-2-[2-[(S)-1-[(R)-1-[(S)-3-amino-3-carbamoylpropanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide were reacted under the same conditions as Example 44 to obtain 170 mg of the title compound as a white solid.

15

¹H NMR(MeOH-d₄, ppm) : δ 7.75(m, 1H), 7.46(m, 1H), 7.25(m, 1H), 6.31(s, 1H), 4.52(m, 1H), 4.18-4.05(m, 3H), 3.77-3.38(m, 5H), 2.89-2.39(m, 4H), 2.29-1.70(m, 10H), 1.26(t, 3H)

ES-MS : 498(M+2)⁺

20 IR(KBr) : 2980, 1615, 1459, 1381 cm⁻¹

25 Example 103 : Synthesis of 1-ethyl-2-[2-[(S)-1-[1-[(R)-1-[3-carbamoyl-(S)-3-[(methanesulfonyl)aminopropanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 162)

a) Synthesis of phenylmethyl 4-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-2-[(tert-butoxy)carbo-nylamino]-4-oxobutanoate:

30

0.3g of the compound II-a obtained in Example 57-b) and 0.346g of (S)-3-[(tert-butoxy)carbonylamino]-3-(benzyloxycarbonyl)propanoic acid were reacted according to the same procedure as Example 11-a) to obtain 0.54g of the title compound as a pale yellow solid.

35

¹H-NMR(CDCl₃, ppm) : δ 7.71(m, 1H), 7.49(m, 1H), 7.32-7.04(m, 6H),
6.30(s, 1H), 5.67(m, 1H), 4.86-4.72(m, 2H), 4.59-4.46(m, 1H),
4.27-4.01(m, 3H), 3.83-3.58(m, 2H), 3.46-3.37(m, 2H), 3.09-2.66
(m, 4H), 2.27-1.69(m, 10H), 1.42(brs, 9H), 1.25(t, 3H)

5 ES-MS : 692(M+Na⁺), 670(M+1)⁺

b) Synthesis of phenylmethyl 2-amino-4-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoate:

10 0.53g of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain 0.40g of the title compound as a pale yellow solid.

¹H-NMR(CDCl₃, ppm) : δ 7.58(m, 2H), 7.40-7.21(m, 6H), 6.32(s, 1H), 5.08
15 -4.96(m, 2H), 4.67-4.48(m, 1H), 4.28-4.08(m, 3H), 3.86-3.67(m, 3H), 3.59-3.38(m, 2H), 2.78(m, 4H), 2.30-1.76(m, 10H), 1.34(t, 3H)

ES-MS : 570(M+1)⁺

20 c) Synthesis of phenylmethyl 4-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-2-[(methylsulfonyl)-amino]-4-oxobutanoate:

25 395mg of the compound obtained in the above b) and 0.08ml of methanesulfonyl chloride were reacted according to the same procedure as Example 1-m) to obtain 300mg of the title compound as a pale yellow solid.

¹H-NMR(CDCl₃, ppm) : δ 7.51(m, 1H), 7.45(m, 1H), 7.39(m, 1H), 7.29(m,
30 3H), 7.10(m, 2H), 6.31(s, 1H), 5.73(m, 1H), 4.87-4.69(m, 2H), 4.63-4.45(m, 1H), 4.29-4.06(m, 3H), 3.26-3.19(m, 1H), 2.96(s, 3H), 2.90-2.67(m, 3H), 2.30-1.79(m, 10H), 1.33(t, 3H)

ES-MS : 670(M+Na⁺), 648(M+1)⁺

35 d) Synthesis of 1-ethyl-2-[2-[(S)-1-[[1-[(R)-1-[3-carbamoyl-(S)-3-

[(methanesulfonyl)amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

300mg of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 25mg of the title compound as a pale yellow solid.

¹H-NMR(MeOH-d₄, ppm) : δ 7.76(m, 1H), 7.49(m, 1H), 7.28(m, 1H), 6.34(s, 1H), 4.53(m, 1H), 4.25-4.09(m, 4H), 3.75-3.38(m, 4H), 2.85-2.61(m, 4H), 2.55(s, 3H) 2.26-1.69(m, 10H), 1.28(t, 3H)

ES-MS : 574(M+1)⁺

IR(KBr) : 2993, 2385, 1681, 1632, 1472, 1389 cm⁻¹

Example 104 : Synthesis of 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl)-(S)-2-[(methanesulfonyl)amino]-4-oxobutanoic acid (Compound 163)

60mg of 1-ethyl-2-[2-[(S)-1-[[1-[(R)-1-[3-carbamoyl-(S)-3-[(methanesulfonyl)amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine obtained in Example 103 was treated according to the same procedure as Example 44 to obtain 15mg of the title compound as a pale yellow solid.

¹H-NMR(MeOH-d₄, ppm) : δ 7.86(m, 1H), 7.52(m, 1H), 7.34(m, 1H), 6.36(s, 1H), 4.53(m, 1H), 4.28-4.10(m, 4H), 3.77-3.39(m, 4H), 2.87-2.56(m, 7H), 2.24-1.68(m, 10H), 1.32(t, 3H)

ES-MS : 575(M+1)⁺

IR(KBr) : 2998, 1628, 1468, 1332 cm⁻¹

Example 105 : Example of 1-ethyl-2-[2-[(S)-1-[(R)-(1-(4-amino-butanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 166)

a) Synthesis of 1-[4-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutyl[(tert-butoxy)formamide:

400mg of the compound II-a obtained in Example 57-b) and 270mg of 4-[(tert-butoxy)carbonylamino]butanoic acid were reacted according to the same procedure as Example 11-a) to obtain 360mg of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.55(m, 2H), 7.26(m, 1H), 6.37(s, 1H), 4.63(m, 1H), 4.28(m, 1H), 4.15(t, 2H, J=7.20Hz), 3.82(m, 1H), 3.66(m, 2H), 3.46(m, 3H), 2.80(m, 4H), 2.52(m, 2H), 2.17(m, 4H), 1.91(m, 2H), 1.42(m, 9H), 1.35(m, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(4-aminobutanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

350mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 170mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.92(m, 1H), 7.34(m, 2H), 6.19(s, 1H), 4.55(m, 1H), 4.16(m, 3H), 3.78(m, 1H), 3.62(m, 2H), 3.41(m, 3H), 2.62(m, 4H), 2.30(m, 2H), 2.07(m, 3H), 1.68(m, 4H), 1.24(m, 3H)

IR(KBr) : 3400, 3000, 1630 cm⁻¹

ES-MS : 467(M+1)⁺

Example 106 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-[(2-piperidinyl)carbonyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamide (Compound 167)

a) Synthesis of tert-butyl-2-[[[(R)-2-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]carbonyl]piperidine carboxylate:

400mg of the compound II-a obtained in Example 57-b) and 300mg of 1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid were reacted according to the same procedure as Example 11-a) to obtain 350mg of the

title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.57(m, 2H), 7.26(m, 1H), 6.35(m, 1H), 4.66(m, 1H), 4.24(m, 1H), 4.14(m, 2H), 3.87(m, 2H), 3.48(m, 2H), 2.80(m, 2H), 2.15(m, 3H), 2.04-1.92(br, 7H), 1.46(m, 9H), 1.35(t, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-[(2-piperidyl)carbonyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

330mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 200mg of the title compound as a yellowish white solid.

¹H NMR(CDCl₃, ppm) : δ 7.62(m, 1H), 7.48(m, 1H), 7.21(m, 1H), 6.32(m, 1H), 4.59(m, 1H), 4.19(m, 4H), 3.85(m, 2H), 3.71(m, 2H), 3.4(m, 3H), 3.12(m, 2H), 2.76(t, 2H), 2.29-2.08(br, 3H), 1.81-1.65(br, 5H), 1.39-1.29(br, 5H), 1.23(m, 3H)

IR(KBr) : 3400, 2880, 1640 cm⁻¹

ES-MS : 493(M+1)⁺

Example 107 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-piperidinylcarbonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamide (Compound 168)

a) Synthesis of tert-butyl 3-[[[R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]carbonyl]piperidinecarboxylate:

300mg of the compound II-a obtained in Example 57-b) and 226mg of 1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid were reacted according to the same procedure as Example 11-a) to obtain 380mg of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.54(m, 2H), 7.24(m, 1H), 6.36(s, 1H), 4.60(m, 1H), 4.26(m, 1H), 4.15(m, 3H), 3.84(m, 2H), 3.71(m, 1H), 3.60(m, 1H), 3.47(m, 1H), 2.80(m, 3H), 2.17(m, 2H), 2.07-1.90(br, 4H).

1.45(m, 9H), 1.35(m, 3H)

ES-MS : 576(M+1)⁺, 598(M+Na)

5 b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[R)-1-(3-piperidinylcarbonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

350mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 210mg of the title compound as a yellowish white solid.

10

IR(KBr) : 3400, 2880, 1640 cm⁻¹

ES-MS : 493(M+1)⁺

15 Example 108 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[[R)-1-[(4-piperidinyl)carbonyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine (Compound 169)

20 a) Synthesis of tert-butyl 4-[[[R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]carbonyl]piperidine carboxylate:

300mg of the compound II-a obtained in Example 57-b) and 226mg of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid were reacted according to the same procedure as Example 11-a) to obtain 200mg of the title compound as a yellow oil.

30 ¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.26(m, 1H), 6.38(s, 1H), 4.54(m, 1H), 4.23(m, 1H), 4.12(m, 3H), 3.80(m, 2H), 3.72(m, 1H), 3.51(m, 2H), 2.79(m, 4H), 2.55(m, 1H), 2.30-2.14(br, 3H), 2.01-1.92(br, 6H), 1.75-1.66(br, 5H), 1.44(m, 9H), 1.32(m, 3H)

ES-MS : 576(M+1)⁺, 598(M+Na)

35 b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[R)-1-[(4-piperidinyl)carbonyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine:

170mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 100mg of the title compound as a yellowish white solid.

5 ¹H NMR(CDCl₃, ppm) : δ 7.84(m, 1H), 7.46(m, 1H), 7.21(m, 1H), 6.25(m, 1H), 4.58(m, 1H), 4.34(m, 2H), 4.16(m, 2H), 3.71(m, 1H), 3.56(m, 2H), 3.12(m, 1H), 2.63(m, 1H), 2.57(m, 3H), 2.05(m, 2H), 1.99(m, 3H), 1.62-1.55(br, 3H), 1.25(m, 3H)

IR(KBr) : 3400, 3000, 1640 cm⁻¹

10 ES-MS : 493(M+1)⁺

Example 109 : Synthesis of 1-methyl-2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonylpyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 170)

15

a) Synthesis of 1-methyl-2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonylpyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

90mg of the compound II-b obtained in Example 58-a) was dissolved in dichloromethane and the resulting solution was cooled to -78 °C. 182μl of triethylamine was added thereto and after 20 minutes, 356 μl of acetyl chloride was added dropwise. After 20 minutes, water was added and the reaction solution was extracted twice with dichloromethane. The extracts were combined, dried over MgSO₄, and then concentrated. 25 The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 69mg of the title compound as a white solid.

30 ¹H NMR(CDCl₃, ppm) : δ 7.68(s, 1H), 7.45(d, 1H), 7.14(d, 1H), 6.32(s, 1H), 4.45(m, 1H), 4.09(m, 1H), 3.80(s, 3H), 3.44(m, 2H), 2.70(m, 2H), 1.97(s, 3H), 2.20-1.65(m, 12H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonylpyrrolidin-2-yl]ethyl]indole-6-carboxamide:

35

210mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 117mg of the title compound as a pale yellow solid.

- 5 ¹H NMR(MeOH-d₄, ppm) : δ 7.88(s, 1H), 7.59(d, 1H), 7.44(d, 1H), 6.46(s, 1H), 4.65-4.57(m, 1H), 4.25-4.15(m, 1H), 3.80(s, 3H), 3.62(m, 2H), 2.88(m, 2H), 2.11(s, 3H), 2.35-1.80(m, 12H)

10 Example 110 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethylindole-6-carboxamide (Compound 171)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethylindole-6-carbonitrile:

15

45mg of the compound II-a obtained in Example 57-b) was dissolved in dichloromethane and the resulting solution was cooled to -78 °C. 34μl of triethylamine was added thereto and after 20 minutes, 18μl of acetyl chloride was added dropwise. After 20 minutes, water was added and the reaction solution was extracted three times with dichloromethane. The extracts were combined, dried over MgSO₄ and then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 38mg of the title compound as a white solid.

25

¹H NMR(CDCl₃, ppm) : δ 7.60-7.48(m, 2H), 7.27(s, 1H), 6.36(s, 1H), 4.57(t, 1H), 4.25(bs, 1H), 4.20-4.08(m, 1H), 3.55-3.36(m, 2H), 2.80(t, 2H), 2.09(s, 3H), 2.40-1.70(m, 12H), 1.34(t, 3H)

30 b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethylindole-6-carboxamide:

800mg of the compound obtained in the above a) was dissolved in 30ml of ethanol solution saturated with HCl gas. The resulting solution was allowed to stand for 2 days at room temperature and then

35

concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vacuum pump. The dried product was then dissolved in 30ml of ethanol solution saturated with NH₃ gas. After 2 days, the resulting solution was concentrated under reduced pressure. The residue was purified with column chromatography [eluent: ethyl acetate/methanol(1:1)] on NH-DM1020 silica to obtain 467mg of the title compound as a white solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.92(s, 1H), 7.65(d, 1H), 7.45(d, 1H), 6.49(s, 1H), 4.62(t, 1H), 4.27(m, 3H), 3.73-3.48(m, 2H), 2.89(t, 2H), 2.10(s, 3H), 2.30-1.80(m, 12H), 1.40(t, 3H)

Example 111 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(2-propylpentanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethylindole-6-carboxamide (Compound 173)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(2-propylpentanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethylindole-6-carbonitrile:

300mg of the compound II-a obtained in Example 57-b) and 0.257 ml of 2-propylpentanoic acid were reacted according to the same procedure as Example 11-a) to obtain 380mg of the title compound.

¹H NMR(CDCl₃, ppm) : δ 7.65-7.47(m, 2H), 7.25(d, 1H), 6.35(s, 1H), 4.68(m, 1H), 4.24(m, 2H), 4.14(q, 2H), 3.88(m, 1H), 3.73(m, 1H), 3.56(m, 1H), 3.41(m, 1H), 2.77(m, 2H), 2.55(m, 1H), 2.37-1.50(m, 10H), 1.43-1.17(m, 11H), 0.87(t, 3H), 0.79(t, 3H)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(2-propylpentanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethylindole-6-carboxamide:

380mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 268mg of the title compound.

¹H NMR(MeOH-d₄, ppm) : δ 7.71(s, 1H), 7.60(d, 1H), 7.25(d, 1H), 6.33(s, 1H), 4.65(m, 1H), 4.21(m, 3H), 3.89(m, 1H), 3.74(m, 1H), 3.60(m, 1H), 3.46(m, 1H), 2.78(m, 2H), 2.54(m, 1H), 2.30-1.50(m, 12H), 1.42-0.92(m, 11H), 0.85(t, 3H), 0.77(t, 3H)

5 ES-MS : 508(M+1)⁺

Example 112 : Synthesis of ethyl 3-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-3-oxopropanoate (Compound 174)

10

a) Synthesis of methyl 3-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-3-oxopropanoate:

15 600mg of the compound II-a obtained in Example 57-b) and 0.353 ml of ethylsuccinyl chloride were reacted according to the same procedure as Example 1-m) to obtain 414mg of the title compound.

20 ¹H NMR(CDCl₃, ppm) : δ 7.52(t, 2H), 7.22(s, 1H), 6.32(s, 1H), 4.65(m, 1H), 4.25(m, 1H), 4.16(q, 2H), 3.72(m, 5H), 3.62(m, 2H), 3.42(m, 3H), 2.77(m, 2H), 2.30-1.80(m, 10H), 1.34(t, 3H)

b) Synthesis of ethyl 3-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-3-oxopropanoate:

25 300mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 97mg of the title compound as a pale yellow solid.

30 ¹H NMR(MeOH-d₄, ppm) : δ 7.87(s, 1H), 7.64(d, 1H, J=8.40Hz), 7.44(d, 1H, J=6.67Hz), 6.49(s, 1H), 4.30(m, 3H), 4.18(q, 2H), 3.82(m, 1H), 3.75-3.50(m, 4H), 3.00-2.75(m, 2H), 2.45-1.75(m, 12H), 1.40(t, 3H), 1.20(t, 3H)

ES-MS : 496(M+1)⁺

35 **Example 113 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(2-carba-**

moylacetyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethylindole-6-carboxamidine (Compound 175)

300mg of methyl 3-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-3-oxopropanoate obtained in
 5 Example 112-a) was treated according to the same procedure as Example 1-n) to obtain 64mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.81(s, 1H), 7.48(d, 1H), 7.33(d, 1H), 6.36(s, 1H), 4.16(m, 3H), 3.73(m, 1H), 3.56(m, 2H), 3.45(m, 2H), 2.75(m, 2H), 2.29-1.50(m, 12H), 1.23(t, 3H)
 10

Example 114 : Synthesis of ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoate (Compound 176)
 15

a) Synthesis of ethyl 4-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoate:

300mg of the compound II-a obtained in Example 57-b) and 250mg of ethyl 3-(chlorocarbonyl)propanoate were reacted according to the same procedure as Example 1-m) to obtain 380mg of the title compound.
 20

¹H NMR(CDCl₃, ppm) : δ 7.82(s, 1H), 7.45(d, 1H, J=8.22Hz), 7.13(d, 1H, J=6.83Hz), 6.32(s, 1H), 4.50(m, 1H), 4.20-3.90(m, 5H), 3.70(m, 1H), 3.56(m, 1H), 3.43(m, 2H), 2.85-2.34(m, 6H), 2.22-1.65(m, 10H), 1.23(t, 3H), 1.13(t, 3H)
 25

b) Synthesis of ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoate:
 30

380mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 117mg of the title compound.

¹H NMR(MeOH-d₄, ppm) : δ 7.82(s, 1H), 7.50(d, 1H), 7.40(d, 1H), 6.30(s, 1H), 4.50(m, 1H), 4.30-3.80(m, 5H), 3.67(m, 1H), 3.60-3.30(m, 3H), 2.90-2.35(m, 6H), 2.20-1.70(m, 10H), 1.30-1.05(m, 6H)

ES-MS : 510(M+1)⁺

5

Example 115 : Synthesis of 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoic acid (Compound 177)

10 153mg of ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-4-oxobutanoate obtained in Example 114 was treated according to the same procedure as Example 44 to obtain 120mg of the title compound as a white foamy solid.

15 ¹H NMR(CDCl₃, ppm) : δ 7.75(s, 1H), 7.40(ddd, 2H, J=8.28Hz, 4.60Hz, 1.61Hz), 6.30(s, 1H), 4.50(m, 1H), 4.10(m, 2H), 3.80-3.30(m, 5H), 2.90-2.55 (m, 2H), 2.55-1.60(m, 14H), 1.25(t, 3H, J=7.14Hz)

ES-MS : 482(M+1)⁺

IR(KBr) : 3190, 2950, 1620 cm⁻¹

20

Example 116 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-sulfanypropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 178)

25 a) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-sulfanypropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

30 105mg of the compound II-a obtained in Example 57-b) and 28μl of 3-sulfanypropanoic acid were reacted according to the same procedure as Example 11-a) to obtain 42mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.61-7.24(m, 3H), 6.37(s, 1H), 4.64(m, 1H), 4.26 (brs, 1H), 4.14(q, 2H, J=6.83Hz), 3.88-3.45(m, 4H), 2.80-2.61(m, 6H), 2.22-1.79(m, 10H), 2.70(t, 3H, J=7.25Hz)

35

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-(3-sulfanyloxypropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

42mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 14mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.78(s, 1H), 7.49-7.29(m, 2H), 6.31(s, 1H), 4.51(m, 1H), 4.19-4.08(m, 3H), 3.71-3.34(m, 4H), 2.82-2.50(m, 6H), 2.10-1.71(m, 10H), 1.25(m, 3H)

IR(KBr) : 3400, 3000, 1640, 1480 cm⁻¹

ES-MS : 470(M+1)⁺

Example 117 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-(3-hydroxybutanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]-ethyl]indole-6-carboxamide (Compound 180)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-(3-hydroxybutanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

0.5g of the compound II-a obtained in Example 57-b) and 0.4ml of 4-hydroxypentanoic acid were reacted according to the same procedure as Example 11-a) to obtain 0.6g of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.61-7.51(m, 2H), 7.27(m, 1H), 6.38(s, 1H), 4.66-4.44(m, 1H), 4.37-4.14(m, 3H), 3.89-3.66(m, 2H), 3.59-3.40(m, 2H), 2.83(m, 2H), 2.59-2.29(m, 3H), 2.24-1.72(m, 10H), 1.38(t, 3H), 1.22(t, 3H)

ES-MS : 473(M+Na⁺), 451(M+1)⁺

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-(3-hydroxybutanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide

0.6g of the compound obtained in the above a) was treated

according to the same procedure as Example 1-n) to obtain 0.6g of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.78(m, 1H), 7.48(m, 1H), 7.29(m, 1H), 6.34
(s, 1H), 4.59-4.35(m, 1H), 4.29-4.07(m, 3H), 3.79-3.41(m, 4H),
2.80(m, 2H), 2.58-2.51(m, 3H), 2.11-1.78(m, 10H), 1.27(t, 3H),
1.10(t, 3H)

ES-MS : 468(M+1)⁺

IR(KBr) : 3167, 2973, 1614, 1508, 1451, 1322 cm⁻¹

Example 118 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-prop-2-enoyl-pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbox-amidine (Compound 182)

320mg of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-(3-chloropropanoyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile obtained in Example 96-a) was treated according to the same procedure as Example 1-n) to obtain 84mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.96(s, 1H), 7.64(d, 1H, J=8.29Hz), 7.44(d, 1H, J=8.38Hz), 6.70(q, 1H), 6.50(s, 1H), 6.29(d, 1H, J=16.85Hz), 5.77(d, 1H, J=12.40Hz), 4.32(m, 3H), 3.70(m, 3H), 3.68(m, 2H), 3.59(m, 2H), 2.90(m, 2H), 2.35-1.80(m, 12H), 1.39(t, 3H)

Example 119 : Synthesis of 1-methyl-2-[2-[(S)-1-[[[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound 183)

a) Synthesis of 1-methyl-2-[2-[(S)-1-[[[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

80mg of the compound II-b obtained in Example 58-a) was dissolved in dichloromethane, and the resulting solution was cooled to -78 °C. 64μl of triethylamine was added thereto and, after 20 minutes, 40μl of methanesulfonyl chloride was added dropwise. After 20 minutes,

water was added and the reaction solution was extracted two times with dichloromethane. The extracts were combined, dried over MgSO_4 and then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(50:1)] to obtain 69mg of the title compound as a yellowish white solid.

^1H NMR(CDCl_3 , ppm) : δ 7.56-7.50(m, 2H), 7.32(d, 1H), 6.38(s, 1H), 4.61(m, 1H), 3.79(bs, 1H), 3.70(s, 3H), 3.60-3.30(m, 2H), 2.98(s, 3H), 2.28(m, 2H), 2.30-1.70(m, 12H)

b) Synthesis of 1-methyl-2-[2-[(S)-1-[[R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

56mg of the compound obtained in the above a) was dissolved in 15ml of ethanol solution saturated with HCl gas. The resulting solution was allowed to stand for one day at room temperature and then concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vacuum pump. The dried product was then dissolved in 15ml of ethanol solution saturated with NH_3 gas. After 2 days, the resulting solution was concentrated under reduced pressure. The residue was purified with column chromatography [eluent: dichloromethane/methanol(3:1)] on NH-DM1020 silica to obtain 41mg of the title compound as a yellowish white solid.

^1H NMR(CDCl_3 , ppm) : δ 8.03(s, 1H), 7.35(m, 2H), 6.19(s, 1H), 4.55(m, 1H), 4.14(bs, 1H), 3.64(s, 3H), 3.43(m, 2H), 2.92(s, 3H), 2.67(m, 2H), 2.30-1.70(m, 12H)

Example 120 : Synthesis of 1-ethyl-2-[2-[(S)-1-[[R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 184)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[[R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

1.00g of the compound II-a obtained in Example 57-b) was dissolved in dichloromethane, and the resulting solution was cooled to 0 °C. 0.75ml of triethylamine was added thereto and after 20 minutes, 0.42 ml of methanesulfonyl chloride was added dropwise. After 20 minutes, water was added and the reaction solution was extracted two times with dichloromethane. The extracts were combined, dried over MgSO₄ and then concentrated. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(50:1)] to obtain 524mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.48(m, 2H), 7.29(d, 1H), 6.37(s, 1H), 4.57(t, 1H), 4.20(bs, 1H), 4.10(m, 2H), 3.49-3.32(m, 2H), 2.99(s, 3H), 2.86-2.70(m, 2H), 2.30-1.65(m, 12H), 1.33(t, 3H)

- b) Synthesis of 1-ethyl-2-[2-[(S)-1-[[[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

430mg of the compound obtained in the above a) was dissolved in 30ml of ethanol solution saturated with HCl gas. The resulting solution was allowed to stand for two days at room temperature and then concentrated under reduced pressure. The remaining HCl was removed for 5 hours by means of a vacuum pump. The dried product was then dissolved in 30ml of ethanol solution saturated with NH₃ gas. After 3 days, the resulting solution was concentrated under reduced pressure. The residue was purified with column chromatography [eluent: ethyl acetate/methanol(1:1)] on NH-DM1020 silica to obtain 184mg of the title compound as an orange solid.

¹H NMR(CDCl₃, ppm) : δ 8.90(bs, 1H), 8.54(bs, 1H), 7.35(s, 1H), 6.15(s, 1H), 4.55(s, 1H), 4.16(m, 1H), 3.70(q, 2H), 2.95(s, 3H), 2.70(m, 2H), 2.30-1.70(m, 12H), 1.18(t, 3H)

Example 121 : Synthesis of ethyl 2-[(S)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinylacetate
(Compound 186)

a) Synthesis of tert-butyl (S)-2-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate:

1.0g of the compound I-a obtained in Example 1-l) and 0.94g of
5 1-(tert-butoxycarbonyl)-L-proline were reacted according to the same
procedure as Example 11-a) to obtain 736mg of the title compound.

¹H NMR(CDCl₃, ppm) : δ 7.61-7.51(m, 2H), 7.30(m, 1H), 6.38(d, 1H,
J=9.95Hz), 4.35(m, 1H), 4.20-4.05(m, 2H), 3.85-3.35(m, 4H),
10 2.80(m, 2H), 2.30-1.70(m, 1H), 1.50-1.29(m, 11H)
IR(KBr) : 3400, 3000, 2220, 1700, 1660 cm⁻¹

b) Synthesis of 1-ethyl-2-[2-[(S)-1-((S)-pyrrolidin-2-ylcarbonyl)pyrroli-
din-2-yl]ethyl]indole-6-carbonitrile:

736mg of the compound obtained in the above a) was treated
according to the same procedure as Example 1-l) to obtain 700mg of the
title compound.

¹H NMR(CDCl₃, ppm) : δ 7.58(s, 1H), 7.54(d, 1H, J=8.28Hz), 7.28(d, 1H,
J=8.27Hz), 6.36(s, 1H), 4.50-4.10(m, 10H), 3.70-3.24(m, 4H), 2.80
(m, 2H), 2.50-1.71(m, 10H), 1.34(t, 3H)

c) Synthesis of ethyl 2-[(S)-2-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-
ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

700mg of the compound obtained in the above b) was treated
according to the same procedure as Example 1-m) to obtain 746mg of the
title compound.

¹H NMR(CDCl₃, ppm) : δ 7.55(t, 1H), 7.24(d, 1H), 6.50(s, 1H), 4.31(m,
1H), 4.17(m, 4H), 3.85(m, 1H), 3.48(m, 3H), 3.22(m, 1H), 2.82(m,
2H), 2.35-1.60(m, 10H), 1.43-1.20(m, 6H)

d) Synthesis of ethyl 2-[(S)-2-[[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-

17]

ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

746mg of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 233mg of the title compound.

¹H NMR(MeOH-d₄, ppm) : δ 7.77(s, 1H), 7.51(d, 1H, J=8.29Hz), 7.32(d, 1H, J=8.30Hz), 6.35(s, 1H), 4.30-4.12(m, 3H), 3.72(m, 1H), 3.58-3.10(m, 5H), 2.77(m, 2H), 2.60(m, 1H), 2.22-1.61(m, 10H), 1.27(t, 3H), 1.12(t, 3H)

ES-MS : 458(M+1)⁺

IR(KBr) : 3200, 1630 cm⁻¹

Example 122 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(carbamoyl-methyl)-5-oxo-pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-indole-6-carboxamidine (Compound 187)

a) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-5-oxopyrrolidin-2-yl]carbonyl]-pyrrolidin-2-yl]ethyl]indole-6-carbonitrile:

202mg of the compound 1-a obtained in Example 1-l) and 107mg of 5-oxopyrrolidine-(R)-2-carboxylic acid were reacted according to the same procedure as Example 11-a) to obtain 136mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.61-7.52(m, 2H), 7.25(m, 1H), 6.50(s, 1H), 6.40(s, 1H), 4.34-4.10(m, 4H), 3.58-3.46(m, 2H), 2.78(t, 2H, J=7.89 Hz), 2.44-1.66(m, 10H), 1.34(t, 3H, J=7.20Hz)

b) Synthesis of ethyl 2-[(R)-5-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]-2-oxopyrrolidinyl]ethanoate:

160mg of the compound obtained in the above a) and 0.052ml of ethyl bromoacetate were dissolved in 3ml of anhydrous tetrahydrofuran, and 19mg of NaH was added thereto. The reaction mixture was heated

under refluxing for 5 hours with stirring. After 0.5ml of water was added dropwise, the reaction solution was evaporated under reduced pressure. The residue was diluted with 150ml of dichloromethane, washed with 30ml of water, dried over sodium sulfate and then filtered. The filtrate was then evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(40:1)]. The fractions containing the desired product were combined and then evaporated to obtain 141mg of the title compound as a viscous oil.

¹H NMR(CDCl₃, ppm) : δ 7.62-7.55(m, 2H), 7.32(m, 1H), 6.41(s, 1H), 4.69(m, 2H), 4.29-4.11(m, 6H), 3.67-3.41(m, 2H), 2.79(t, 2H, J=7.98Hz), 2.56-1.65(m, 10H), 1.37(t, 3H, J=7.21Hz), 1.24(t, 3H, J=7.09Hz)

c) Synthesis of 1-ethyl-2-[2-[(S)-1-[(R)-1-(carbamoylmethyl)-5-oxo-pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

141mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 25mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.80(s, 1H), 7.58-7.31(m, 2H), 6.40(s, 1H), 4.59(m, 1H), 4.21-4.14(m, 4H), 3.64-3.32(m, 3H), 2.82-2.73(m, 2H), 2.37-1.79(m, 10H), 1.30(t, 3H, J=7.15Hz)

ES-MS : 453(M+1)⁺

Example 123 : Synthesis of 2-[(R)-5-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]-2-oxopyrrolidinyl]acetic acid (Compound 188)

12mg of 1-ethyl-2-[2-[(S)-1-[(R)-1-(carbamoylmethyl)-5-oxo-pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide obtained in Example 122-c) was treated according to the same procedure as Example 44 to obtain 6mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.79(s, 1H), 7.54-7.30(m, 2H), 6.38(s, 1H),
4.34(d, 1H, J=17.12Hz), 4.22-4.05(m, 3H), 3.63-3.34(m, 3H), 3.13
(d, 1H, J=17.17Hz), 2.81-2.70(m, 2H), 2.37-1.71(m, 10H), 1.29(t,
3H, J=7.15Hz)

ES-MS : 454(M+1)⁺

Example 124 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(2-piperidyl)-
carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound
189)

a) Synthesis of tert-butyl-2-[[[(S)-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-
pyrrolidinyl]carbonyl]piperilidine carboxylate:

1.7g of 1-ethyl-2-[[[(S)-pyrrolidin-2-yl]ethyl]indole-6-carbonitrile
was reacted with 1.75g of 1-(tert-butoxycarbonyl)-pipecolinic acid
according to the same procedure as Example 11-a) to obtain 1.17g of the
title compound as a pale yellow foam.

¹H NMR(CDCl₃, ppm) : δ 7.63-7.53(m, 2H), 7.29-7.26(m, 1H), 6.37(s, 1H),
4.77(br, 1H), 4.31(br, 1H), 4.19-4.14(m, 2H), 3.93-3.89(m, 1H),
3.74-3.70(m, 1H), 3.52-3.48(m, 2H), 2.80-2.75(m, 2H), 2.19-2.14
(m, 1H), 2.01-1.62(m, 11H), 1.49-1.42(m, 9H), 1.35(t, 3H,
J=7.20Hz)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(2-piperidyl)carbonyl]pyrrolidin-2-
yl]ethyl]indole-6-carboxamidine:

40mg of the compound obtained in the above a) was treated
according to the same procedure as Example 1-n) to obtain 19mg of the
title compound as a white solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.77(s, 1H), 7.52-7.30(m, 2H), 6.33(s, 1H),
4.20-4.01(m, 3H), 3.56(m, 1H), 3.47-3.31(m, 2H), 3.02-2.50(m,
4H), 2.23-1.04(m, 12H), 1.26(m, 3H)

IR(KBr) : 3400, 2980, 1640, 1550, 1480 cm^{-1}

ES-MS : 396(M+1)⁺

5 Example 125 : Synthesis of ethyl 2-[2-[[[S]-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]carbonyl]piperidinyl]ethanoate
(Compound 190)

a) Synthesis of ethyl 2-[2-[[[S]-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidin-2-yl]carbonyl]piperidinyl]ethanoate:

10 120mg of tert-butyl-2-[[[S]-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]carbonyl]piperidine carboxylate obtained in Example 124-a) was treated according to the same procedure as Example 1-l) to obtain 86mg of the white solid product, which was then reacted with ethyl
15 2-bromoacetate according to the same procedure as Example 1-m) to obtain 85mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.58(s, 1H), 7.56-7.27(m, 2H), 6.44(d, 1H, J=7.62Hz), 3.71(brs, 2H), 3.60-3.49(m, 2H), 3.40-3.28(m, 1H),
20 3.03-2.56(m, 4H), 2.36-1.65(m, 12H), 1.36(t, 3H, J=8.58Hz), 1.27-1.17(m, 3H)

b) Synthesis of ethyl 2-[2-[[[S]-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidin-2-yl]carbonyl]piperidinyl]ethanoate :

25 78mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 32mg of the title compound as a pale yellow solid.

30 ¹H NMR(MeOH-d₄, ppm) : δ 7.79(s, 1H), 7.56-7.31(m, 2H), 6.36(s, 1H), 4.27-4.11(m, 3H), 4.02-3.83(m, 2H), 3.69-3.21(m, 5H), 3.94-2.50(m, 4H), 2.22-1.46(m, 12H), 1.29(m, 3H), 1.14-1.05(m, 3H)

IR(KBr) : 3400, 2990, 1755, 1690, 1640, 1550, 1485 cm^{-1}

ES-MS : 482(M+1)⁺

Example 126 : Synthesis of ethyl 2-[2-[[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]piperidiny]carbonyl]piperidiny]acetate (Compound 191)

- 5 a) Synthesis of tert-butyl 2-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-piperidiny]carbonyl]piperidine carboxylate:

600mg of 1-ethyl-2-[2-((S)-piperidiny]ethyl]indole-6-carbonitrile and 500mg of 1-[(tert-butoxy)carbonyl]piperidine-2-carboxylic acid were
10 reacted according to the same procedure as Example 11-a) to obtain 300 mg of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.57(m, 2H), 7.30(m, 1H), 6.35(s, 1H), 4.95(br, 1H), 4.12(m, 2H), 3.90(br, 1H), 3.72(m, 1H), 2.71(m, 2H), 2.21(m, 1H), 1.84(m, 2H), 1.45(m, 9H), 1.33(m, 3H)
15

- b) Synthesis of 1-ethyl-2-[2-[1-[[[(S)-2-piperidiny]carbonyl]-2-piperidyl]ethyl]indole-6-carbonitrile:

20 280mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain 210mg of the title compound as a pale yellow solid.

- 25 c) Synthesis of ethyl 2-[2-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-piperidyl]carbonyl]piperidiny]acetate:

200mg of the compound obtained in the above b) and 0.085ml of ethyl 2-bromoacetate were reacted according to the same procedure as Example 1-m) to obtain 120mg of the title compound as a pale yellow oil.
30

¹H NMR(CDCl₃, ppm) : δ 7.56(m, 2H), 7.29(m, 1H), 6.38(s, 1H), 5.03(br, 1H), 4.11(m, 4H), 3.40(2H), 3.02(m, 2H), 2.75(m, 1H), 2.60(m, 2H), 2.20(m, 1H), 1.73(m, 3H), 1.32(m, 5H), 1.26(m, 3H), 1.17(m, 3H)
35

ES-MS : 479(M+1)⁺, 501(M+Na)

d) Synthesis of ethyl 2-[2-[[[S]-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]piperidiny]carbonyl]piperidiny]acetate:

110mg of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 40mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.75(m, 1H), 7.56(m, 1H), 7.32(m, 1H), 6.34(s, 1H), 5.01(br, 1H), 4.12(m, 4H), 3.46(1H), 3.39(m, 2H), 3.02(m, 2H), 2.75(m, 1H), 2.59(m, 2H), 2.18(m, 1H), 1.76(m, 3H), 1.67(br, 6H), 1.32(m, 5H), 1.17(m, 3H)

IR(KBr) : 3400, 2900, 1610, 1460 cm⁻¹

ES-MS : 497(M+2), 519(M+Na)

Example 127 : Synthesis of methyl-2-[2-[[[S]-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidiny]carbonyl]piperidiny]acetate (Compound 192)

a) Synthesis of methyl-2-[2-[[[S]-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidiny]carbonyl]piperidiny]acetate:

1g of tert-butyl-2-[[[S]-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidiny]carbonyl]piperidine carboxylate obtained in Example 124-a) was treated according to the same procedure as Example 1-l) to obtain 1-ethyl-2-[2-[[[S]-1-[(2-piperidiny]carbonyl]pyrrolidin-2-yl)ethyl]indole-6-carbonitrile, which was then reacted with methyl 2-bromoacetate according to the same procedure as Example 1-m) to obtain 631mg of the title compound as a pale yellow oil.

ES-MS : 450(M+1)

¹H NMR(CDCl₃, ppm) : δ 7.58-7.53(m, 2H), 7.30-7.27(m, 1H), 6.46-6.43(m, 1H), 4.35(br, 1H), 4.17-4.14(m, 2H), 3.67-3.64(m, 4H), 3.54-3.48(m, 2H), 3.40-3.32(m, 1H), 2.98(br, 1H), 2.79(br, 2H), 2.60-2.56(m, 1H), 2.24-2.21(m, 1H), 2.00-1.98(m, 4H), 1.74-1.64(m, 8H), 1.35(br, 3H)

b) Synthesis of methyl-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]piperidinyl]acetate:

630mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 200mg of the title compound as a pale yellow foam.

ES-MS : 468(M+1)⁺

¹H NMR(MeOH-d₄, ppm) : δ 7.79(s, 1H), 7.57-7.51(m, 1H), 7.37-7.31(m, 1H), 6.37(s, 1H), 4.21-4.18(m, 3H), 3.62-3.58(m, 1H), 3.58-3.54(m, 3H), 3.49-3.45(m, 2H), 3.29-3.23(m, 2H), 2.89-2.85(m, 1H), 2.76-2.72(m, 2H), 2.51-2.44(m, 1H), 2.18-2.05(m, 1H), 1.94-1.86(m, 3H), 1.74-1.69(m, 4H), 1.55-1.50(m, 4H), 1.26-1.19(m, 3H)

Example 128 : Synthesis of 2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]piperidinyl]acetic acid (Compound 193)

30mg of methyl-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]piperidinyl]acetate obtained in Example 127-b) was treated according to the same procedure as Example 44 to obtain 17 mg of the title compound as a pale yellow solid.

ES-MS : 454(M+1)⁺

¹H NMR(MeOH-d₄, ppm) : δ 7.80-7.78(m, 1H), 7.55-7.50(m, 1H), 7.35-7.31(m, 1H), 6.37(s, 1H), 4.22-4.18(m, 3H), 3.75-3.69(m, 1H), 3.61-3.50(m, 2H), 2.99-2.91(m, 3H), 2.78-2.75(m, 2H), 2.47-2.42(m, 1H), 2.12-1.55(m, 12H), 1.25-1.19(m, 3H)

IR(KBr) : 3420, 2980, 1580 cm⁻¹

Example 129 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(3-piperidinyl)-carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide (Compound 194)

a) Synthesis of tert-butyl 3-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]

-pyrrolidiny]carbonyl]piperidine carboxylate:

130mg of the compound I-a obtained in Example 1-l) and 1-
[(tert-butoxy)carbonyl]piperidine-3-carboxylic acid were reacted according
5 to the same procedure as Example 11-a) to obtain 76mg of the title
compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.60-7.29(m, 3H), 6.40(d, 1H, J=3.62Hz), 4.28-
4.02(m, 5H), 3.71-3.42(m, 2H), 2.77(m, 4H), 2.53-1.59(m, 11H),
10 1.46(s, 9H), 1.38(t, 3H, J=7.10Hz)

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(3-piperidiny]carbonyl]pyrrolidin-2-
yl]ethyl]indole-6-carboxamidine:

71mg of the compound obtained in the above a) was treated
15 according to the same procedure as Example 1-n) to obtain 35mg of the
title compound as a pale yellow solid.

¹H-NMR(MeOH-d₄, ppm) : δ 7.80(s, 1H), 7.54-7.31(m, 2H), 6.36(s, 1H),
20 4.22-4.02(m, 3H), 3.52(m, 2H), 2.92-2.28(m, 6H), 2.18-1.41(m,
11H)

IR(KBr) : 3380, 2990, 1630, 1540, 1480 cm⁻¹

ES-MS : 396(M+1)⁺

25 Example 130 : Synthesis of 1-ethyl-2-[2-[(S)-1-[(4-piperidinyl)-
carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine (Compound
195)

a) Synthesis of tert-butyl 4-[[[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-
30 ethyl]pyrrolidiny]carbonyl]piperidine carboxylate:

148mg of the compound I-a obtained in Example 1-l) and 1-
[(tert-butoxy)carbonyl]piperidine-4-carboxylic acid were reacted accor-
35 ding to the same procedure as Example 11-a) to obtain 63mg of the title
compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.58-7.24(m, 3H), 6.39(s, 1H), 4.30-3.95(m, 5H),
3.54(m, 2H), 2.89-2.68(m, 4H), 2.52-1.58(m, 11H), 1.46(s, 9H),
1.36(t, 3H, J=7.25Hz)

5

b) Synthesis of 1-ethyl-2-[2-[(S)-1-[(4-piperidiny)carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide:

59mg of the compound obtained in the above a) was treated
10 according to the same procedure as Example 1-n) to obtain 26mg of the
title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.81-7.32(m, 3H), 6.37(s, 1H), 4.24-4.06(m,
4H), 3.53(m, 2H), 3.00-2.53(m, 7H), 2.18-1.50(m, 9H)
15 IR(KBr) : 3300, 2980, 1620, 1530, 1470 cm⁻¹
ES-MS : 396(M+1)⁺

Example 131 : Synthesis of ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]pyrrolidine-2-carboxylate (Compound 196)
20

a) Synthesis of ethyl 1-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-oxoethyl]pyrrolidine-2-carboxylate:

25 109mg of 1-ethyl-2-[2-[(S)-1-(2-chloroacetyl)pyrrolidin-2-yl]ethyl]-indole-6-carbonitrile was treated according to the same procedure as Example 45-b) to obtain 133mg of the title compound as a viscous brown oil.

30 ¹H NMR(CDCl₃, ppm) : δ 7.51-7.54(m, 2H), 7.32(m, 1H), 6.41(s, 1H), 4.20-4.13(m, 5H), 3.61(dd, J=14.52Hz, 6.38Hz), 3.50(m, 2H), 3.33(t, 1H, J=15.46Hz), 3.12(brs, 1H), 2.83-2.74(m, 2H), 2.38-1.70(m, 11H), 1.36(t, 3H, J=7.17Hz), 1.24(t, 3H, J=6.71Hz)

35 b) Synthesis of ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]

-pyrrolidiny]-2-oxoethyl]pyrrolidine-2-carboxylate:

130mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 35mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.78(s, 1H), 7.52-7.30(m, 2H), 6.36(s, 1H), 4.21-3.97(m, 5H), 3.56-3.27(m, 5H), 3.01(m, 1H), 2.83-2.74(m, 2H), 2.56-1.72(m, 11H), 1.29(t, 3H, J=7.12Hz), 1.08(t, 3H, J=7.04Hz)

IR(KBr) : 3350, 2980, 1730, 1620, 1520, 1460, 1160 cm⁻¹

ES-MS : 468(M+1)⁺

Example 132 : Synthesis of 1-[2-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidiny]-2-oxoethyl]pyrrolidine-2-carboxylic acid (Compound 197)

22mg ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidiny]-2-oxoethyl]pyrrolidine-2-carboxylate was treated according to the same procedure as Example 44 to obtain 15mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.88-7.32(m, 3H), 6.42-6.33(m, 1H), 4.25-4.13(m, 3H), 3.50-3.08(m, 5H), 3.00-2.86(m, 1H), 2.76(m, 2H), 2.47-1.51(m, 11H), 1.28(t, 3H, J=7.20Hz)

IR(KBr) : 3350, 2960, 1700, 1650, 1450 cm⁻¹

ES-MS : 440(M+1)⁺

Example 133 : Synthesis of ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidiny]-2-oxoethyl]piperidine-2-carboxylate (Compound 198)

a) Synthesis of ethyl 1-[2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidiny]-2-oxoethyl]piperidine-2-carboxylate:

112mg of 1-ethyl-2-[2-[(S)-1-(2-chloroacetyl)pyrrolidin-2-yl]ethyl]-indole-6-carbonitrile was treated according to the same procedure as Example 45-b) to obtain 140mg of the title compound as a viscous brown oil.

5

¹H NMR(CDCl₃, ppm) : δ 7.61-7.54(m, 2H), 7.30(m, 1H), 6.41(d, 1H, J=3.07Hz), 4.28-4.13(m, 5H), 3.73-3.30(m, 4H), 3.19(t, 1H), 3.03-2.95(m, 1H), 2.79(t, 2H, J=7.98Hz), 2.64-1.60(m, 13H), 1.36(t, 3H, J=7.22Hz), 1.29-1.23(m, 3H)

10

b) Synthesis of ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-oxoethyl]piperidine-2-carboxylate:

136mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 43mg of the title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.77(s, 1H), 7.53-7.30(m, 2H), 6.35(s, 1H), 4.21-4.02(m, 5H), 3.59-3.03(m, 5H), 2.96-2.88(m, 1H), 2.79-2.69(m, 2H), 2.45-1.37(m, 13H), 1.29(t, 3H, J=7.13Hz), 1.18-1.13(m, 3H)

20

IR(KBr) : 3300, 2960, 1730, 1620, 1520, 1460, 1180 cm⁻¹

ES-MS : 481.62(M+1)⁺

25 Example 134 : Synthesis of 1-[2-[(S)-2-[2-(6-amidino-1-ethyl-indol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]piperidine-2-carboxylic acid (Compound 199)

27mg of ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-pyrrolidinyl]-2-oxoethyl]piperidine-2-carboxylate was treated according to the same procedure as Example 44 to obtain 14mg of the title compound as a pale yellow solid.

30

¹H NMR(MeOH-d₄, ppm) : δ 7.71(s, 1H), 7.55-7.27(m, 2H), 6.29(s, 1H), 4.20-4.06(m, 3H), 3.61-3.35(m, 3H), 3.41(d, 1H, J=14.55Hz), 2.82

35

(d, 1H, J=14.65Hz), 2.93-2.64(m, 3H), 2.28-1.50(m, 13H), 1.27-1.19(m, 3H)

ES-MS : 454(M+1)⁺

5 Example 135 : Synthesis of ethyl 2-[2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-6-amidinoindolyl]-acetate (Compound 222)

a) Synthesis of 2-(hydroxymethyl)indole-6-carbonitrile:

10

10g of ethyl 6-cyanoindole-2-carboxylate was treated according to the same procedure as Example 1-e) to obtain 6.8g of the title compound as a yellow solid.

15 ¹H NMR(MeOH-d₄, ppm) : δ 7.63(s, 1H), 7.52(d, 1H), 7.15(m, 1H), 6.38(s, 1H), 4.67(s, 2H)

b) Synthesis of tert-butyl (S)-2-[2-(6-cyanoindol-2-yl)vinyl]pyrrolidine carboxylate:

20

1g of 2-(hydroxymethyl)indole-6-carbonitrile was treated according to the same procedure as Examples 1-f) and 1-m) to obtain 800mg of the title compound as a yellow oil.

25 ¹H NMR(CDCl₃, ppm) : δ 7.47(m, 2H), 7.24(m, 1H), 6.33(s, 1H), 4.40(m, 1H), 3.36(m, 2H), 2.15-1.70(m, 6H), 1.47(m, 9H)

c) Synthesis of tert-butyl (S)-2-[2-(6-cyanoindol-2-yl)ethyl]pyrrolidine carboxylate:

30

800mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-k) to obtain 620mg of the title compound as a yellow oil.

35 ¹H NMR(CDCl₃, ppm) : δ 7.66(s, 1H), 7.50(t, 1H), 7.20(m, 1H), 6.21(s,

1H), 3.92(m, 1H), 3.32(m, 2H), 2.80(m, 2H), 2.1-1.7(m, 6H), 1.6-1.35(m, 9H)

- 5 d) Synthesis of ethyl 2-[6-cyano-2-[2-[(S)-1-[(tert-butoxy)carbonyl]-pyrrolidin-2-yl]ethyl]indolyl]acetate:

620mg of the compound obtained in the above c) and 0.3ml of ethyl 2-bromoacetate were reacted with NaH in the presence of N,N-dimethylformamide to obtain 850mg of the title compound as a brown oil.

10

¹H NMR(CDCl₃, ppm) : δ 7.60(s, 1H), 7.51(s, 1H), 7.36(d, 1H), 6.46(s, 1H), 4.84(s, 2H), 4.32-4.20(m, 2H), 3.98(m, 1H), 3.43-3.27(m, 2H), 2.80-2.65(m, 2H), 1.95-1.67(m, 6H), 1.60-1.42(m, 9H), 1.37-1.23(m, 3H)

15

- e) Synthesis of ethyl 2-[6-cyano-2-[2-[(S)-1-[(R)-1-[(tert-butoxy)-carbonyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indolyl]acetate:

800mg of the compound obtained in the above d) was treated according to the same procedure as Examples 1-l) and 11-a) to obtain 340mg of the title compound as a pale yellow solid.

20

¹H NMR(MeOH-d₄, ppm) : δ 7.63(s, 1H), 7.50(d, 1H), 7.20(d, 1H), 6.42(m, 1H), 4.68(s, 2H), 4.30-4.20(m, 1H), 4.10(m, 2H), 3.67-3.57(m, 1H), 3.51(m, 2H), 3.32(m, 2H), 2.10-1.60(m, 2H), 1.36-1.25(m, 9H), 1.10(m, 3H)

25

- f) Synthesis of ethyl 2-[2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-6-cyanoindolyl]acetate:

30

300mg of the compound obtained in the above e) was treated according to the same procedure as Examples 1-l) and 1-m) to obtain 180mg of the title compound as a yellow solid.

35 ¹H NMR(CDCl₃, ppm) : δ 7.60(m, 1H), 7.50(s, 1H), 7.34(m, 1H), 6.47(s,

1H), 4.86(m, 2H), 4.35-4.17(m, 3H), 3.89(m, 1H), 3.70(m, 2H),
3.54(m, 2H), 2.30-1.90(m, 9H), 1.35(m, 6H)

g) Synthesis of ethyl 2-[2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-6-amidinoindolyl]acetate:

150mg of the compound obtained in the above f) was treated according to the same procedure as Example 1-n) to obtain 80mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.50(m, 2H), 6.32(s, 1H), 4.97(s, 2H), 4.65(m, 1H), 4.15(m, 3H), 3.86(m, 1H), 3.68(m, 2H), 3.39(m, 2H), 2.70(m, 2H), 2.19-1.82(m, 12H), 1.22(m, 3H)

ES-MS : 482(M+1)⁺

Example 136 : Synthesis of 2-[2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-1-(carbamoylmethyl)indole-6-carboxamide (Compound 224)

30mg of ethyl 2-[2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-6-cyanoindolyl]acetate obtained in Example 135-g) was treated according to the same procedure as Example 1-n) to obtain 30mg of the title compound as a yellowish white solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.74(s, 1H), 7.59(m, 1H), 7.36(m, 1H), 6.39(s, 1H), 4.87(s, 2H), 4.59(m, 1H), 4.29(m, 1H), 3.73(m, 3H), 2.75(m, 2H), 2.21(m, 2H), 2.09(s, 3H), 2.00-1.89(m, 9H)

ES-MS : 453(M+1)⁺

Example 137 : Synthesis of 2-[2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-6-amidinoindolyl]acetic acid (Compound 225)

40mg of ethyl 2-[2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]-6-amidinoindolyl]acetate obtained in

Example 135 was treated according to the same procedure as Example 44 to obtain 15mg of the title compound as a white solid.

¹H NMR(MeOH-d₄+CDCl₃, ppm) : δ 7.46(m, 2H), 7.28(m, 1H), 6.37(s, 1H),
4.64(s, 2H), 4.53(s, 1H), 4.19(br, 1H), 3.79(m, 1H), 3.64(m, 3H),
2.75(m, 2H), 2.17(m, 3H), 2.03(s, 3H), 2.01-1.78(m, 7H), 1.28(m,
2H)

ES-MS : 451(M+1)⁺

Example 138 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(5-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 242)

a) Synthesis of ethyl 5-bromoindole-2-carboxylate:

In a 500ml flask, 14g of 4-bromophenylhydrazine hydrochloride was dissolved in 170ml of ethanol, and 1.2ml of sulfuric acid and 8.5ml of ethyl pyruvate were added. The reaction mixture was stirred for about 2 hours at room temperature and evaporated under reduced pressure to dryness. To the residue was added 23ml of polyphosphoric acid, and the resulting solution was then stirred for 2 hours at 100°C-110°C. After water was added, the reaction solution was neutralized with saturated aqueous NaHCO₃ solution and then extracted two times with ethyl acetate. The extracts were combined, dried over MgSO₄ and then evaporated. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(9:1)] to obtain 10g of the title compound as a brown solid.

¹H NMR(CDCl₃, ppm) : δ 9.03(br, 1H), 7.82(s, 1H), 7.41(m, 1H), 7.31(m,
1H), 7.14(s, 1H), 4.40(q, 2H, J=7.1Hz), 1.41(t, 3H, J=7.1Hz)

b) Synthesis of ethyl 5-bromo-1-methylindole-2-carboxylate:

4.5g of the compound obtained in the above a) and 2.1ml of iodomethane were reacted according to the same procedure as Example

1-d) to obtain 5.9g of the title compound as a yellow oil.

c) Synthesis of ethyl 5-cyano-1-methylindole-2-carboxylate:

5 In a 500ml flask, 8.7g of the compound obtained in the above b) was dissolved in 430ml of 1-methylpyrrolidin-2-one, and 4.1g of CuCN was added thereto. The reaction mixture was stirred for 14 hours at 190°C-200°C, cooled to room temperature and then filtered. To the filtrate was added water, and the reaction solution was extracted two
10 times with chloroform. The extracts were combined, dried over MgSO₄ and then evaporated. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(3:1)] to obtain 6.5g of the title compound as a brown solid.

15 d) Synthesis of 1-methyl-2-(hydroxymethyl)indole-5-carbonitrile:

 6g of the compound obtained in the above c) was treated according to the same procedure as Example 1-e) to obtain 2.4g of the title compound as a yellowish white solid.

20

¹H NMR(CDCl₃, ppm) : δ 7.90(s, 1H), 7.42(m, 1H), 7.33(m, 1H), 6.53(s, 1H), 4.83(s, 2H), 3.84(s, 3H)
IR(KBr) : 3250, 2200, 1600, 1480 cm⁻¹

25 e) Synthesis of (5-cyano-1-methyl-2-indolyl)methyltriphenylphosphonium bromide:

 2.4g of the compound obtained in the above d) was treated according to the same procedure as Example 1-f) to obtain 5.3g of the
30 title compound as a pale pink solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.82(m, 3H), 7.62(m, 15H), 6.26(m, 1H), 5.19(d, 2H), 3.08(s, 3H)

35 f) Synthesis of tert-butyl (S)-2-[2-(5-cyano-1-methylindol-2-yl)vinyl]-

pyrrolidine carboxylate:

5g of the compound obtained in the above e) was treated according to the same procedure as Example 1-j) to obtain 1.6g of the title compound as a yellow oil.

g) Synthesis of tert-butyl (S)-2-[2-(5-cyano-1-methylindol-2-yl)ethyl]-pyrrolidine carboxylate:

1.4g of the compound obtained in the above f) was treated according to the same procedure as Example 1-k) to obtain 1.3g of the title compound as a yellow oil.

h) Synthesis of 1-methyl-2-((S)-2-pyrrolidin-2-ylethyl)indole-5-carbonitrile:

1.2g of the compound obtained in the above g) was treated according to the same procedure as Example 1-l) to obtain 710mg of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.82(s, 1H), 7.35(m, 1H), 7.26(m, 1H), 6.32(s, 1H), 3.66(s, 3H), 3.19(m, 1H), 3.06(m, 2H), 2.97(m, 1H), 2.81(m, 2H), 1.94(m, 5H)

i) Synthesis of tert-butyl (R)-2-[[[S)-2-[2-(5-cyano-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate:

700mg of the compound obtained in the above h) was treated according to the same procedure as Example 11-a) to obtain 1g of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.85(m, 1H), 7.36(m, 1H), 7.27(m, 1H), 6.34(s, 1H), 4.11(m, 1H), 3.80(m, 1H), 3.68(s, 3H), 3.61(m, 2H), 3.43(m, 3H), 2.82(m, 2H), 2.16-1.87(m, 9H), 1.42(s, 9H)

j) Synthesis of 1-methyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]indole-5-carbonitrile:

5 1g of the compound obtained in the above i) was treated according to the same procedure as Example 1-l) to obtain 730mg of the title compound as a yellow oil.

k) Synthesis of methyl 2-[(R)-2-[(S)-2-[2-(5-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

10

720mg of the compound obtained in the above j) and 0.35ml of ethyl 2-bromoacetate were reacted according to the same procedure as Example 1-m) to obtain 680mg of the title compound as a pale yellow oil.

15 ¹H NMR(CDCl₃, ppm) : δ 7.87(s, 1H), 7.44(m, 1H), 7.29(m, 1H), 6.40(s, 1H), 4.23(m, 1H), 4.12(m, 2H), 3.87(m, 1H), 3.72(s, 3H), 3.53(m, 2H), 3.22(m, 1H), 2.82(m, 3H), 2.01-1.89(m, 9H), 1.22(t, 3H, J=7.1Hz)

20 l) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(5-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

670mg of the compound obtained in the above k) was treated according to the same procedure as Example 1-n) to obtain 200g of the title compound as a yellowish white solid.

25 ¹H NMR(CDCl₃, ppm) : δ 7.98(s, 1H), 7.49(m, 1H), 7.30(m, 1H), 6.56(s, 1H), 4.70-4.39(br, 2H), 4.28(m, 1H), 4.12(q, 2H), 3.81(m, 1H), 3.66(s, 3H), 3.60(m, 2H), 3.29(m, 1H), 2.77(m, 3H), 2.35(m, 1H), 2.17(m, 1H), 2.00-1.78(m, 9H), 1.24(t, 3H)

30

IR(KBr) : 3300, 2900, 1720, 1620 cm⁻¹

ES-MS : 454(M+1)⁺, 476(M+Na)

35 Example 139 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[(S)-2-(5-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]-

acetate (Compound 243)

a) Synthesis of ethyl 5-bromo-1-ethylindole-2-carboxylate:

5 4.5g of ethyl 5-bromoindole-2-carboxylate and 2.7ml of iodoethane were reacted according to the same procedure as Example 1-d) to obtain 5.2g of the title compound as a yellow oil.

b) Synthesis of ethyl 5-cyano-1-ethylindole-2-carboxylate:

10 In a 500ml flask, 7.7g of the compound obtained in the above a) was dissolved in 360ml of 1-methylpyrrolidin-2-one, and 3.5g of CuCN was added thereto. The reaction mixture was stirred for 14 hours at 190°C-200°C, cooled to room temperature and then filtered. To the
15 filtrate was added water, and the reaction solution was extracted two times with chloroform. The extracts were combined, dried over MgSO₄ and then evaporated. The residue was purified with silica gel column chromatography [eluent: n-hexane/ethyl acetate(3:1)] to obtain 5.4g of the
20 title compound as a brown solid.

c) Synthesis of 1-ethyl-2-(hydroxymethyl)indole-5-carbonitrile:

 5g of the compound obtained in the above b) was treated according to the same procedure as Example 1-e) to obtain 2.9g of the
25 title compound as a yellowish white solid.

¹H NMR(CDCl₃, ppm) : δ 7.91(s, 1H), 7.44(m, 1H), 7.38(m, 1H), 6.52(s, 1H), 4.83(s, 2H), 4.32(q, 2H, J=7.2Hz), 1.42(t, 3H, J=7.2Hz)
IR(KBr) : 3450, 2200, 1600, 1480 cm⁻¹

30

d) Synthesis of (5-cyano-1-ethyl-2-indolyl)methyltriphenylphosphonium bromide:

 2.8g of the compound obtained in the above c) was treated
35 according to the same procedure as Example 1-f) to obtain 6g of the title

compound as a pale pink solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.92(m, 3H), 7.74(m, 15H), 6.29(m, 1H), 3.78
(q, 2H, J=7.1Hz), 3.33(m, 2H), 1.12(t, 3H, J=7.1Hz)

5

e) Synthesis of tert-butyl (S)-2-[2-(5-cyano-1-ethylindol-2-yl)vinyl]-pyrrolidine carboxylate:

5g of the compound obtained in the above d) was treated
according to the same procedure as Example 1-j) to obtain 1.7g of the
title compound as a yellow oil.

10

f) Synthesis of tert-butyl (S)-2-[2-(5-cyano-1-ethylindol-2-yl)ethyl]-pyrrolidine carboxylate:

15

1.6g of the compound obtained in the above e) was treated
according to the same procedure as Example 1-k) to obtain 1.5g of the
title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.85(s, 1H), 7.38(m, 1H), 7.26(m, 1H), 6.35(s,
1H), 4.14(q, 2H, J=7.2Hz), 3.95(br, 1H), 3.37(m, 2H), 2.75(m, 2H),
1.92-1.76(m, 6H), 1.47(s, 9H), 1.35(t, 3H, J=7.2Hz)

20

g) Synthesis of 1-ethyl-2-((S)-2-pyrrolidin-2-ylethyl)indole-5-carbonitrile:

25

1.4g of the compound obtained in the above f) was treated
according to the same procedure as Example 1-l) to obtain 940mg of the
title compound as a yellow oil.

30

h) Synthesis of tert-butyl (R)-2-[[[(S)-2-[2-(5-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate:

930mg of the compound obtained in the above g) was treated
according to the same procedure as Example 11-a) to obtain 960mg of the

35

title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.85(m, 1H), 7.35(m, 1H), 7.28(m, 1H), 6.36(s, 1H), 4.15(m, 3H), 3.80(m, 1H), 3.62(m, 2H), 3.43(m, 3H), 2.79(m, 2H), 2.11-1.85(m, 9H), 1.42(s, 9H)

i) Synthesis of 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]indole-5-carbonitrile:

960mg of the compound obtained in the above h) was treated according to the same procedure as Example 1-l) to obtain 650mg of the title compound as a yellow oil.

j) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(5-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

640mg of the compound obtained in the above i) and 0.3ml of ethyl 2-bromoacetate were reacted according to the same procedure as Example 1-m) to obtain 650mg of the title compound as a pale yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.80(s, 1H), 7.38(m, 1H), 7.28(m, 1H), 6.40(s, 1H), 4.27(m, 1H), 4.13(m, 4H), 3.87(m, 1H), 3.56(m, 2H), 3.22(m, 1H), 2.78(m, 3H), 2.02-1.86(m, 9H), 1.35(t, 3H, J=7.1Hz), 1.22(t, 3H, J=7.1Hz)

k) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(5-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

630mg of the compound obtained in the above j) was treated according to the same procedure as Example 1-n) to obtain 150mg of the title compound as a yellowish white solid.

¹H NMR(CDCl₃, ppm) : δ 8.15(s, 1H), 7.55(m, 1H), 7.30(m, 1H), 6.71(s, 1H), 6.10-5.80(br, 2H), 4.38(m, 1H), 4.11(m, 4H), 3.73(m, 1H), 3.44(m, 2H), 3.38(m, 1H), 2.72(m, 3H), 2.45(m, 1H), 2.20(m, 1H),

1.99-1.70(m, 9H), 1.26(m, 6H)

IR(KBr) : 3200, 3000, 1740, 1620 cm^{-1}

ES-MS : 468(M+1)⁺

5 Example 140 : Synthesis of 6-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carboxamide (Compound 244)

1g of 7-cyanonaphthalene-3-methyltriphenylphosphonium bromide and 390mg of (S)-1-(t-butoxycarbonyl)-2-pyrrolidinal were dissolved in a
10 mixed solvent of 15ml of tetrahydrofuran and 15ml of ethanol, and 360 μl of DBU (1,8-diazabicyclo[5.4.0]undec-7ene) was added at room temperature. The reaction solution was stirred overnight at room temperature and distilled under reduced pressure to remove the solvent. The residue was purified with silica gel column chromatography [eluent:
15 n-hexane/ethyl acetate(3:1)]. The fractions containing the desired product were combined and distilled under reduced pressure to obtain the product, tert-butyl (S)-2-[2-(6-cyano-2-naphthyl)vinyl]pyrrolidine carboxylate. 410mg of this product thus obtained was dissolved in 15ml of ethanol and then hydrogenated in the presence of 50mg of Pd/C(10% w/w)
20 for 2 hours under normal pressure with stirring. The reaction solution was filtered under reduced pressure to remove Pd/C, and the filtrate was distilled under reduced pressure and dried under reduced pressure. The residue was dissolved in 10ml of dichloromethane, and 3ml of trifluoroacetic acid was added. The mixture thereby obtained was stirred
25 overnight at room temperature, and excess of dichloromethane was added thereto. The organic layer was separated, washed with aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate and then filtered under reduced pressure. The filtrate was distilled under reduced pressure to obtain 320mg of the oily product, 6-((S)-2-pyrrolidin-2-yl)ethyl]naphthalene-2-carbonitrile. 85mg of the resulting oily product
30 was then treated according to the same procedure as Example 1-m) to obtain 50mg of the compound 6-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carbonitrile, which was then treated according to the same procedure as Example 1-n) to obtain 30mg of the title compound
35 as a yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 8.20(d, 1H), 7.83(m, 2H), 7.68(m, 2H), 7.37(d, 1H), 7.21-7.12(m, 5H), 6.98(d, 1H), 6.76(d, 1H), 4.05(m, 1H), 3.59(m, 2H), 3.37(m, 4H), 2.70(t, 2H), 2.15(m, 1H), 1.93-1.79(m, 7H), 1.70(m, 1H)

5

Example 141 : Synthesis of methyl 2-[(R)-2-[(S)-2-[2-(6-amidino-2-naphthyl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 245)

- 10 a) Synthesis of methyl 2-[(R)-2-[(S)-2-[2-(6-cyano-2-naphthyl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

250mg of 6-((S)-2-pyrrolidin-2-ylethyl)naphthalene-2-carbonitrile was treated according to the same procedure as Example 11-a) to obtain 256mg of tert-butyl (R)-2-[(S)-2-[2-(6-cyano-2-naphthyl)ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate. 150mg of the compound thereby obtained was reacted according to the same procedure as Example 1-l) to obtain 134mg of 6-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]-ethyl]naphthalene-2-carbonitrile. Thereafter, 130mg of the compound thus obtained was treated according to the same procedure as Example 1-m) to obtain 129mg of the title compound as a yellow solid.

20

¹H NMR(CDCl₃, ppm) : δ 8.17(s, 1H), 7.92- 7.79(m, 2H), 7.73(s, 1H), 7.50(m, 2H), 4.19(bs, 1H)

25

- b) Synthesis of methyl 2-[(R)-2-[(S)-2-[2-(6-amidino-2-naphthyl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

124mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-n) to obtain 48mg of the title compound as a pale yellow solid.

30

¹H NMR(MeOH-d₄, ppm) : δ 8.35(s, 1H), 7.95(m, 2H), 7.89(m, 2H), 7.54(d, 1H, J=11.73Hz), 4.20-4.00(m, 3H), 3.79(m, 1H), 3.62(m, 2H), 3.46(d, 2H, J=19.11Hz), 3.20(m, 1H), 3.00(m, 1H), 2.98-2.70(m, 3H),

35

2.33-1.70(m, 11H)

ES-MS : 451(M+1)⁺

5 Example 142 : Synthesis of 7-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carboxamide (Compound 246)

a) Synthesis of tert-butyl (S)-2-(2-(7-cyano-2-naphthyl)vinyl)pyrrolidine carboxylate:

10 5.6g of 7-cyanonaphthalene-2-methyltriphenylphosphonium bromide was reacted according to the same procedure as Example 1-j) to obtain 2.9g of the title compound.

15 ¹H NMR(CDCl₃, ppm) : δ 8.24-7.54(m, 6H), 6.55(bs, 1H), 6.30(bs, 1H), 4.51(bd, 1H), 3.49(s, 2H), 2.17-1.82(m, 4H), 1.83-1.26(m, 9H)

b) Synthesis of 7-((S)-2-pyrrolidin-2-ylethyl)naphthalene-2-carbonitrile:

20 2.9g of the compound obtained in the above a) was treated according to the same procedure as Example 1-k) to obtain 2.7g of the product, which was then treated according to the same procedure as Example 1-l) to obtain 1.6g of the title compound as a yellow oil.

25 ¹H NMR(CDCl₃, ppm) : δ 7.79(s, 1H), 7.76(d, 1H, J=8.46Hz), 7.68(d, 1H, J=8.42Hz), 7.54-7.48(t, 2H), 7.37(d, 1H, J=8.43Hz), 3.49(t, 1H), 3.26(m, 2H), 2.91-2.82(m, 2H), 2.30-1.68(m, 6H)

ES-MS : 251(M+1)⁺

30 c) Synthesis of 7-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carbonitrile:

445mg of the compound obtained in the above b) and 0.47ml of phenyl acetylchloride were reacted according to the same procedure as Example 1-m) to obtain 298mg of the title compound.

¹H NMR(CDCl₃, ppm) : δ 8.14(s, 1H), 7.86-7.78(q, 2H), 7.67(s, 1H), 7.55-7.51(m, 2H), 7.32-6.92(m, 5H), 4.21(m, 1H), 3.64(s, 1H), 3.46(m, 2H), 2.80(t, 2H, J=8.16Hz), 2.33(m, 1H), 2.04-1.59(m, 5H)

- 5 d) Synthesis of 7-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carboxamide:

270mg of the compound obtained in the above c) was treated according to the same procedure as Example 1-n) to obtain 128mg of the
10 title compound as a pale yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 8.08(s, 1H), 7.77-7.61(m, 4H), 7.34-7.32(d, 1H, J=8.38Hz), 7.20-7.13(m, 3H), 6.94(m, 1H), 6.73(d, 1H), 4.08
15 (bs, 1H), 3.56(s, 2H), 3.45-3.30(m, 2H), 2.67(t, 2H), 2.20-1.50(m, 6H)

ES-MS : 386(M+1)⁺

20 Example 143 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(7-amidino-2-naphthyl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate
(Compound 247)

- a) Synthesis of 7-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carbonitrile:

25 450mg of 7-((S)-2-pyrrolidin-2-ylethyl)naphthalene-2-carbonitrile obtained in Example 142-b) was treated according to the same procedure as Example 11-a) to obtain 643mg of tert-butyl (R)-2-[[[(S)-2-[2-(7-cyano-2-naphthyl)ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate, which was then treated according to the same procedure as Example 1-l)
30 to obtain 472mg of the title compound as a brown oil.

¹H NMR(CDCl₃, ppm) : δ 8.17(s, 1H), 7.90(d, 1H, J=8.83Hz), 7.79(d, 1H, J=8.49Hz), 7.73(s, 1H), 7.49(d, 2H), 4.35(t, 1H), 4.02(m, 1H), 3.52(m, 1H), 3.32(m, 2H), 2.76(m, 2H), 2.36(m, 1H), 2.23(m, 1H),
35 2.10-1.80(m, 8H), 1.74-1.60(m, 1H)

ES-MS : 348(M+1)⁺

b) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(7-cyano-2-naphthyl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

5

572mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-m) to obtain 700mg of the title compound as a yellow solid.

10 ¹H NMR(CDCl₃, ppm) : δ 8.18(s, 1H), 7.90-7.70(m, 3H), 7.50(m, 2H), 4.01(m, 2H), 3.89(m, 1H), 3.67(m, 1H), 3.54-3.12(m, 5H), 3.05(m, 1H), 2.92(m, 1H), 2.73(m, 2H), 2.20-1.50(m, 10H), 1.06(t, 3H)

ES-MS : 434(M+1)⁺, 456(M+Na)

15 c) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(7-amidino-2-naphthyl)ethyl]-pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

650mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 148mg of the title compound as a pale yellow solid.

20

¹H NMR(MeOH-d₄, ppm) : δ 8.08(s, 1H), 7.78-7.76(m, 4H), 7.34(m, 1H), 4.00(m, 2H), 3.90(m, 1H), 3.65(m, 1H), 3.57-3.15(m, 4H), 3.07(m, 1H), 2.88(m, 1H), 2.65(m, 2H), 2.17-1.50(m, 10H), 1.07(t, 3H)

25 ES-MS : 451(M+1)⁺, 474(M+Na)

IR(KBr) : 3200, 1220 cm⁻¹

Example 144 : Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]benzo[b]furan-5-carboxamide (Compound 248)

30

a) Synthesis of ethyl 2-(4-bromo-2-formylphenoxy)acetate:

35

In a 1 l flask, 30g of 5-bromosalicyl aldehyde was stirred in 500 ml of acetone solvent at room temperature, and then 26.8g of K₂CO₃ was slowly added thereto. After the mixture thereby obtained was stirred for

30 minutes, 21.5ml of ethyl bromoacetate was slowly added dropwise thereto and the reaction mixture was refluxed for 2 hours with stirring. After the reaction was completed, the reaction solution was evaporated. To the residue was added dichloromethane and the resulting precipitate was filtered and washed two times with water. The organic layers were combined, dried over MgSO_4 and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 43g of the title compound as a yellow liquid.

^1H NMR(CDCl_3 , ppm) : δ 10.45(s, 1H), 7.95(d, 1H, $J=2.59\text{Hz}$), 7.60(dd, 1H, $J=8.79\text{Hz}$, 2.61Hz), 6.75(d, 1H, $J=8.62\text{Hz}$), 4.75(s, 2H), 4.20(q, 2H, $J=7.14\text{Hz}$), 1.25(t, 3H, $J=7.15\text{Hz}$)
ES-MS : 288(M+1)⁺

b) Synthesis of ethyl 5-bromobenzo[d]furan-2-carboxylate:

In a 1 l flask, 2.96g of Na was slowly added to 250ml of ethanol solvent, and this mixture was stirred for 30 minutes. 42g of the compound obtained in the above a) was slowly added dropwise thereto at room temperature. The reaction solution was stirred for 2 hours and then evaporated under reduced pressure. The residue was extracted two times with ethyl acetate. The combined organic layer was dried over MgSO_4 and then evaporated to obtain 11.7g of the title compound as a yellow solid.

^1H NMR(CDCl_3 , ppm) : δ 7.80(s, 1H), 7.45(m, 2H), 4.40(q, 2H, $J=7.13\text{Hz}$), 1.40(t, 3H, $J=7.13\text{Hz}$)
ES-MS : 270(M+1)⁺

c) Synthesis of ethyl 5-cyanobenzo[d]furan-2-carboxylate:

In a 250ml flask, 24.7g of the compound obtained in the above b) was dissolved in 100ml of N-methylpyrrolidinone, and 16.53g of CuCN

and 1.48g of CuSO_4 catalyst were added thereto. The reaction mixture was refluxed for one hour at $200-220^\circ\text{C}$ with stirring. The reaction solution was then stirred for 30 minutes at room temperature. After excessive amount of water was added, the reaction solution was stirred and then filtered. The residue was washed three times with ethyl acetate. The organic layers were combined, dried over MgSO_4 and then evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:5)]. The fractions containing the desired product were combined and then evaporated to obtain 6.39g of the title compound as a white solid.

^1H NMR(CDCl_3 , ppm) : δ 8.05(s, 1H), 7.70(m, 2H), 7.55(s, 1H), 4.45(q, 2H, $J=7.10\text{Hz}$), 1.45(t, 3H, $J=7.12\text{Hz}$)

ES-MS : 216(M+1)⁺

d) Synthesis of 2-(hydroxymethyl)benzo[b]furan-5-carbonitrile:

6.39g of the compound obtained in the above c) was treated according to the same procedure as Example 1-e) to obtain a stoichiometric amount of the title compound as a white solid.

^1H NMR(CDCl_3 , ppm) : δ 8.0(s, 1H), 7.60(s, 2H), 6.75(s, 1H), 4.80(s, 1H), 4.65(s, 1H)

ES-MS : 174(M+1)⁺

e) Synthesis of benzo[b]furan-5-carbonitrile-2-methyltriphenylphosphonium bromide:

5.34g of the compound obtained in the above d) was treated according to the same procedure as Example 1-f) to obtain 14.8g of the title compound as a white solid.

^1H NMR(CDCl_3 , ppm) : δ 7.95-7.60(m, 16H), 7.45(m, 1H), 7.25(m, 2H), 6.05(d, 2H)

f) Synthesis of tert-butyl (S)-2-[2-(5-cyanobenzo[d]furan-2-yl)vinyl]-pyrrolidine carboxylate:

11.8g of the compound obtained in the above e) was treated according to the same procedure as Example 1-j) to obtain 3.99g of the title compound as a fluorescent yellow liquid.

¹H NMR(CDCl₃, ppm) : δ 7.80(s, 1H), 7.45(m, 2H), 6.55(s, 1H), 6.50-6.10(m, 2H), 4.45(m, 1H), 3.45(br, 2H), 2.0-1.70(m, 4H), 1.40(br, 9H)
ES-MS : 339(M+1)⁺

g) Synthesis of tert-butyl (S)-2-[2-(5-cyanobenzo[d]furan-2-yl)ethyl]-pyrrolidine carboxylate:

2.09g of the compound obtained in the above f) was treated according to the same procedure as Example 1-k) to obtain 1.75g of the title compound as a colorless liquid.

¹H NMR(CDCl₃, ppm) : δ 7.80(s, 1H), 7.45(m, 2H), 6.50(s, 1H), 3.90(m, 1H), 3.40(m, 2H), 2.80(m, 2H), 2.30-1.60(m, 6H), 1.40(br, 9H)

h) Synthesis of 2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-5-carbonitrile:

1.55g of the compound obtained in the above g) was treated according to the same procedure as Example 1-l) to obtain a stoichiometric amount of the title compound as a colorless foamy solid.

¹H NMR(CDCl₃, ppm) : δ 9.30(br, 1H), 7.75(s, 1H), 7.40(m, 2H), 3.50(m, 1H), 3.25(m, 2H), 2.90(m, 2H), 2.35-1.80(m, 4H), 1.70(m, 1H)
ES-MS : 241(M+1)⁺

i) Synthesis of 1-((S)-2-(2-(5-ethynylbenzo[d]furan-2-yl)ethyl)pyrrolidin-2-yl)-2-phenylethan-1-one:

220mg of 2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-5-carbonitrile obtained in the above h) and 180mg of phenylacetyl chloride were reacted according to the same procedure as Example 1-m) to obtain 200mg of the title compound as a colorless liquid.

¹H NMR(CDCl₃, ppm) : δ 7.80(s, 2H), 7.45(m, 2H), 7.25(m, 5H), 6.55(s, 1H), 4.25(m, 1H), 3.65(m, 2H), 3.45(m, 2H), 2.80(m, 2H), 2.30(m, 1H), 2.10-1.80(m, 3H), 1.70(m, 2H)

ES-MS : 358(M+1)⁺

j) Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]benzo[b]furan-5-carboxamide:

190mg of the compound obtained in the above i) was treated according to the same procedure as Example 1-n) to obtain 180mg of the title compound as a colorless foamy solid.

¹H NMR(CDCl₃, ppm) : δ 7.70(s, 1H), 7.55-7.10(m, 7H), 6.50(s, 1H), 4.25(m, 1H), 3.65(s, 2H), 3.45(m, 1H), 2.80(t, 2H, J=7.80Hz), 2.30(m, 1H), 2.10-1.80(m, 3H), 1.70(m, 2H)

ES-MS : 376(M+1)⁺

IR(KBr) : 3300, 2950, 2800, 1650 cm⁻¹

Example 145 : Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]vinyl]benzo[b]furan-5-carboxamide (Compound 249)

a) Synthesis of 2-(2-pyrrolidin-(S)-ylvinyl)benzo[b]furan-5-carbonitrile:

490mg of tert-butyl (S)-2-[2-(5-cyanobenzo[d]furan-2-yl)vinyl]-pyrrolidine carboxylate obtained in Example 144-f) was treated according to the same procedure as Example 1-l) to obtain a stoichiometric amount of the title compound as a colorless solid.

¹H NMR(CDCl₃, ppm) : δ 7.75(m, 1H), 7.45(m, 2H), 6.65-6.30(m, 3H), 4.10(m, 1H), 3.35-3.15(m, 2H), 2.40-1.75(m, 4H)

ES-MS : 239(M+1)⁺

b) Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]vinyl]benzo-
[b]furan-5-carbonitrile:

5

450mg of the compound obtained in the above a) and 0.3ml of phenylacetyl chloride were reacted according to the same procedure as Example 1-m) to obtain 344mg of the title compound as a colorless foamy solid.

10

¹H NMR(CDCl₃, ppm) : δ 7.75(m, 1H), 7.45(m, 2H), 7.40-7.15(m, 5H), 6.65-6.20(m, 3H), 4.75(m, 1H), 3.80-3.40(m, 4H), 2.25-1.75(m, 4H)

ES-MS : 357(M+1)⁺

15

c) Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]vinyl]benzo-
[b]furan-5-carboxamide:

223mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-n) to obtain 190mg of the title compound as a colorless foamy solid.

¹H NMR(CDCl₃, ppm) : δ 7.75(m, 2H), 7.60-7.0(m, 7H), 6.70-6.20(m, 3H), 5.20-4.80(br, 3H), 3.75-3.40(m, 4H), 2.25-1.75(m, 4H)

25 ES-MS : 374(M+1)⁺

IR(KBr) : 3200, 2950, 2850, 1650 cm⁻¹

Example 146 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(5-amidino-
benzo[d]furan-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate
(Compound 250)

30

a) Synthesis of tert-butyl (R)-2-[(S)-2-[2-(5-cyanobenzo[d]furan-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidine carboxylate:

35

447mg of 2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-5-carbonitrile

obtained in Example 144-h was treated according to the same procedure as Example 11-a) to obtain 370mg of the title compound as a colorless foamy solid.

5 ¹H NMR(CDCl₃, ppm) : δ 7.80(m, 1H), 7.40(m, 2H), 6.55(d, 1H), 4.40(m, 1H), 4.20(m, 1H), 3.85-3.30(m, 4H), 2.85(m, 2H), 2.45-1.60(m, 10H), 1.40(br, 9H)

ES-MS : 438(M+1)⁺

10 b) Synthesis of 2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]-ethyl]benzo[b]furan-5-carbonitrile:

240mg of the compound obtained in the above a) was treated according to the same procedure as Example 1-l) to obtain 200mg of the
15 title compound as a pale yellow foamy solid.

¹H NMR(CDCl₃, ppm) : δ 7.75(s, 1H), 7.40(m, 2H), 6.55(s, 1H), 4.55(m, 1H), 4.15(m, 1H), 3.60(m, 1H), 3.40(m, 3H), 2.75(m, 2H), 2.45(m, 1H), 2.25(m, 1H), 2.15-1.70(m, 8H)

20

c) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(5-cyanobenzo[d]furan-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

203mg of the compound obtained in the above b) was treated according to the same procedure as Example 1-m) to obtain 248mg of the
25 title compound as a pale yellow liquid.

¹H NMR(CDCl₃, ppm) : δ 7.80(s, 1H), 7.45(m, 2H), 6.65(s, 1H), 4.30-4.0(m, 3H), 3.85(m, 1H), 3.65-3.35(m, 4H), 3.20(m, 1H), 2.80(m, 3H),
30 2.30(m, 1H), 2.15(m, 1H), 2.10-1.60(m, 8H), 1.25(t, 3H, J=7.14Hz)

ES-MS : 424(M+1)⁺

d) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(5-amidinobenzo[d]furan-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate :

35

200mg of the compound obtained in the above c) was treated

according to the same procedure as Example 1-n) to obtain 100mg of the title compound as a pale yellowish white foamy solid.

¹H NMR(CDCl₃, ppm) : δ 7.90(s, 1H), 7.50(m, 2H), 6.65(s, 1H), 4.45(m, 1H), 4.20-3.95(m, 4H), 3.65(m, 1H), 3.50(m, 1H), 3.35(m, 1H), 3.15(m, 1H), 2.80(m, 1H), 2.45(m, 1H), 2.25(m, 1H), 2.10-1.70(m, 9H), 1.15(t, 3H, J=7.10Hz)

ES-MS : 441(M+1)⁺

IR(KBr) : 3200, 2950, 1750, 1670 cm⁻¹

10

Example 147 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-
benzo[d]furan-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate
(Compound 251) and 2-[2-[(S)-1-[(R)-1-(carbamoylmethyl)pyrro-
lidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]benzo[b]furan-6-carboxa-
midine

15

a) Synthesis of 3-bromo-1-(2-bromoprop-2-enyloxy)benzene:

In a 1 l flask, 25g of 5-bromophenol was stirred in 250ml of dimethylformamide at room temperature, and 39.9g of K₂CO₃ was slowly added thereto. After the mixture thereby obtained was stirred for 30 minutes, 22.4ml of 2,3-dibromopropene was slowly added dropwise thereto and the reaction mixture was refluxed for 2 hours with stirring. After the reaction was completed, excessive amount of water was added to the reaction solution, which was then extracted three times with ether. The combined organic layer was dried over MgSO₄ and then evaporated. The residue was purified with silica gel column chromatography [eluent: hexane]. The fractions containing the desired product were combined and then evaporated to obtain 37.1g of the title compound as a yellow liquid.

30

¹H NMR(CDCl₃, ppm) : δ 7.10(m, 3H), 6.82(m, 1H), 5.96(s, 1H), 5.68(s, 1H), 4.60(s, 2H)

b) Synthesis of 5-bromo-2-(2-bromoprop-2-enyl)phenol:

35

In a 500ml flask, 240ml of 1N-BBr₃ was slowly added over one hour to 37g of the compound obtained in the above a) in 250ml of CS₂ solvent, and this mixture was then stirred for 6 hours. The reaction was quenched with 5N HCl at 0°C. The reaction solution was evaporated under reduced pressure and extracted two times with ether. The combined organic layer was dried over MgSO₄ and then evaporated to obtain 24.0g of the title compound as a yellow oil.

¹H NMR(CDCl₃, ppm) : δ 7.10-6.90(m, 3H), 5.55(d, 1H, J=1.40Hz), 5.50(d, 1H, J=1.60Hz), 5.05(s, 1H), 3.70(s, 2H)

c) Synthesis of 6-bromo-2-methylbenzo[b]furan:

In a 250ml flask, 24.0g of the compound obtained in the above b) was dissolved in 50ml of ethanol at room temperature, and 200ml of 2M NaOEt was slowly added dropwise thereto. The reaction solution was refluxed for 5 hours with stirring and then evaporated under reduced pressure. The residue was extracted three times with ethyl acetate. The combined organic layer was dried over MgSO₄ and then evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:30)]. The fractions containing the desired product were combined and then evaporated to obtain 11.3g of the title compound as a pale yellow liquid.

¹H NMR(CDCl₃, ppm) : δ 7.75(s, 1H), 7.30(s, 2H), 6.30(s, 1H), 2.40(s, 3H)

d) Synthesis of 2-methylbenzo[b]furan-6-carbonitrile:

11.3g of the compound obtained in the above c) was treated according to the same procedure as Example 144-c) to obtain 381mg of the title compound as a pale yellow solid.

¹H NMR(CDCl₃, ppm) : δ 7.69(s, 1H), 7.50(ddd, 2H, J=24.96Hz, 8.02Hz, 1.04Hz), 6.45(s, 1H), 2.50(s, 2H)

e) Synthesis of 2-(bromomethyl)benzo[b]furan-6-carbonitrile:

380mg of the compound obtained in the above d) was dissolved in 100ml of carbon tetrachloride, and 472mg of NBS (N-bromosuccinimide) was added thereto. The reaction solution was refluxed for 6 hours with stirring and then evaporated under reduced pressure. The residue was then extracted three times with ethyl acetate. The combined organic layer was dried over MgSO_4 and evaporated under reduced pressure. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/ n-hexane(1:7)]. The fractions containing the desired product were combined and then evaporated to obtain 520mg of the title compound as a pale yellow solid.

$^1\text{H NMR}(\text{CDCl}_3, \text{ppm}) : \delta$ 7.75(s, 1H), 7.55(m, 2H), 6.80(s, 1H), 4.60(s, 2H)

f) Synthesis of benzo[b]furan-6-carbonitrile-2-methyl-triphenylphosphonium bromide:

520mg of the compound obtained in the above e) was treated according to the same procedure as Example 1-f) to obtain 770mg of the title compound as a pale yellow solid.

$^1\text{H NMR}(\text{CDCl}_3, \text{ppm}) : \delta$ 7.90-7.35(m, 19H), 6.10(d, 2H)

g) Synthesis of tert-butyl (S)-2-[2-(5-cyanobenzo[d]furan-2-yl)vinyl]-pyrrolidine carboxylate:

770mg of the compound obtained in the above f) was treated according to the same procedure as Example 1-j) to obtain 308mg of the title compound as a fluorescent yellow liquid.

$^1\text{H NMR}(\text{CDCl}_3, \text{ppm}) : \delta$ 7.70(m, 1H), 7.50(m, 2H), 6.70-6.20(m, 3H), 4.50(m, 1H), 3.45(br, 2H), 2.25-1.70(m, 4H), 1.40(br, 9H)

h) Synthesis of 2-((2S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-6-carboni-

trile:

308mg of the compound obtained in the above g) was treated according to the same procedure as Example 1-k) to obtain 270mg of the yellow liquid product, which was then treated according to the same procedure as Example 1-l) to obtain 229mg of the title compound as a yellow liquid.

¹H NMR(CDCl₃, ppm) : δ 7.61(s, 1H), 7.45(dd, 2H, J=23.51Hz, 8.02Hz), 6.50(s, 1H), 3.50(m, 1H), 3.30(m, 2H), 2.92(m, 2H), 2.49-1.88(m, 5H), 1.71(m, 1H)

ES-MS : 241(M+1)⁺

i) Synthesis of tert-butyl (R)-2-[[[(S)-2-[2-(6-cyanobenzo[d]furan-2-yl)-ethyl]pyrrolidiny]carbonyl]pyrrolidine carboxylate:

228mg of 2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-6-carbonitrile obtained in the above h) was treated according to the same procedure as Example 11-a) to obtain 167mg of the title compound as a yellowish white foamy solid.

¹H NMR(CDCl₃, ppm) : δ 7.80(m, 1H), 7.40(m, 2H), 6.55(d, 1H), 4.40(m, 1H), 4.20(m, 1H), 3.85-3.30(m, 4H), 2.85(m, 2H), 2.45-1.60(m, 10H), 1.40(br, 9H)

j) Synthesis of ethyl 2-[(R)-2-[[[(S)-2-[2-(6-cyanobenzo[d]furan-2-yl)-ethyl]pyrrolidiny]carbonyl]pyrrolidiny]acetate:

167mg of the compound obtained in the above i) was treated according to the same procedure as Example 1-l) to obtain 100mg of the white foamy product, which was then reacted with ethyl 2-bromoacetate according to the same procedure as Example 1-m) to obtain 60mg of the title compound as a white foamy solid.

¹H NMR(CDCl₃, ppm) : δ 7.75(s, 1H), 7.55(m, 2H), 6.80(s, 1H), 4.30-4.0

(m, 3H), 3.85(m, 1H), 3.50(m, 2H), 3.20(m, 1H), 2.80(m, 3H),
2.40-1.60(m, 12H), 1.25(t, 3H, J=7.14Hz)

5 k) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidinobenzo[d]furan-2-yl)-ethyl]pyrrolidiny]carbonyl]pyrrolidiny]acetate :

60mg of the compound obtained in the above j) was treated according to the same procedure as Example 1-n) to obtain 4.2mg of the title compound as a white foamy solid.

10

¹H NMR(CDCl₃, ppm) : δ 7.65(s, 1H), 7.45(m, 2H), 6.60(s, 1H), 5.05(br, 3H), 4.30-4.0(m, 3H), 3.85(m, 1H), 3.50(m, 4H), 3.20(m, 1H), 2.80(m, 3H), 2.40-1.60(m, 10H), 1.47(t, 3H, J=7.14Hz)

ES-MS : 442(M+2)⁺

15

l) Synthesis of 2-[2-[(S)-1-[(R)-1-(carbamoylmethyl)pyrrolidin-2-yl]-carbonyl]pyrrolidin-2-yl]ethyl]benzo[b]furan-6-carboxamidine:

20 60mg of ethyl 2-[(R)-2-[(S)-2-[2-(6-cyanobenzo[d]furan-2-yl)-ethyl]pyrrolidiny]carbonyl]pyrrolidiny]acetate obtained in the above j) was treated according to the same procedure as Example 1-n) to obtain 3.2mg of the title compound as a yellow foamy solid.

25 ¹H NMR(CD₃OD, ppm) : δ 7.75(s, 1H), 7.50(m, 2H), 6.55(s, 1H), 4.05(m, 1H), 3.60-3.25(m, 3H), 3.10(m, 1H), 3.0-2.60(m, 3H), 2.40(m, 1H), 2.15(m, 1H), 2.15-1.55(m, 10H)

ES-MS : 413(M+2)⁺

30 Example 148 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-3-methylbenzo[d]furan-2-yl)ethyl]pyrrolidiny]carbonyl]pyrrolidiny]-acetate (Compound 252)

a) Synthesis of 1-(4-bromo-2-hydroxyphenyl)ethan-1-one:

35

In a 1 l flask, 25g of 5-bromoanisole was stirred in 250ml of CS₂

solvent at 0°C, and 12.4ml of acetyl chloride was added and 53.5g of AlCl₃ was slowly added portionwise thereto. After the addition was completed, the reaction solution was refluxed for one hour with stirring. The reaction was quenched with 2N HCl. Excessive amount of water was added and the reaction solution was extracted three times with ethyl acetate. The combined organic layer was dried over MgSO₄ and then evaporated. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:10)]. The fractions containing the desired product were combined and then evaporated to obtain 7.68g of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 12.3(s, 1H), 7.57(d, 1H, J=8.56Hz), 7.17(d, 1H, J=1.92Hz), 7.04(dd, 1H, J=8.49Hz, 1.98Hz)

ES-MS : 237(M+1)⁺

b) Synthesis of ethyl 2-(5-bromo-2-acetylphenoxy)acetate:

7.68g of the compound obtained in the above a) was treated in acetone solvent according to the same procedure as Example 42 to obtain 3.58g of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.65(d, 1H, J=8.34Hz), 7.20(dd, 1H, J=8.32Hz, 1.76Hz), 6.95(d, 1H, J=1.64Hz), 4.70(s, 2H), 4.25(q, 2H, J=7.15 Hz), 2.65(s, 3H), 1.35(t, 3H, J=7.11Hz)

c) Synthesis of ethyl 6-bromo-3-methylbenzo[d]furan-2-carboxylate:

3.58g of the compound obtained in the above b) was treated according to the same procedure as Example 144-b) to obtain 1.26g of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.70(s, 1H), 7.40(m, 2H), 4.40(q, 2H, J=7.13Hz), 2.50(s, 3H), 1.40(t, 3H, J=7.13Hz)

ES-MS : 283(M+1)⁺

d) Synthesis of ethyl 6-cyano-3-methylbenzo[d]furan-2-carboxylate:

7.52g of the compound obtained in the above c) was treated according to the same procedure as Example 144-c) to obtain 790mg of the title compound as a white solid.

^1H NMR(CDCl_3 , ppm) : δ 7.85(s, 1H), 7.70(d, 1H, $J=8.24\text{Hz}$), 7.55(dd, 1H, $J=8.15\text{Hz}$, 1.26Hz), 4.45(q, 2H, $J=7.14\text{Hz}$), 2.60(s, 3H), 1.45(t, 3H, $J=7.12\text{Hz}$)

ES-MS : 230($M+1$) $^+$

e) Synthesis of 2-(hydroxymethyl)-3-methylbenzo[b]furan-6-carbonitrile:

789mg of the compound obtained in the above d) was treated according to the same procedure as Example 1-e) to obtain 459mg of the title compound as a yellow solid.

^1H NMR(CDCl_3 , ppm) : δ 7.75(s, 1H), 7.55(d, 1H, $J=7.96\text{Hz}$), 7.40(d, 1H, $J=8.03\text{Hz}$), 4.60(s, 2H), 2.15(s, 3H)

f) Synthesis of benzo[b]furan-6-carbonitrile-2-methyl-triphenylphosphonium bromide:

459mg of the compound obtained in the above e) was treated according to the same procedure as Example 1-f) to obtain 855mg of the title compound as a yellow solid.

^1H NMR(CDCl_3 , ppm) : δ 7.95-7.35(m, 18H), 5.85(d, 2H), 2.25(s, 3H)

g) Synthesis of tert-butyl (S)-2-[2-(6-cyano-3-methylbenzo[d]furan-2-yl)vinyl]pyrrolidine carboxylate:

850mg of the compound obtained in the above f) was treated according to the same procedure as Example 1-j) to obtain 344mg of the title compound as a fluorescent yellow liquid.

¹H NMR(CDCl₃, ppm) : δ 7.65(s, 1H), 7.45(m, 2H), 6.40(br, 2H), 4.50(m, 1H), 3.45(br, 2H), 2.25(s, 3H), 2.05-1.70(m, 4H), 1.40(br, 9H)

h) Synthesis of 3-methyl-2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]furan-6-carbonitrile:

344mg of the compound obtained in the above g) was treated according to the same procedure as Example 1-k) to obtain 340mg of the colorless liquid product, which was then treated according to the same procedure as Example 1-l) to obtain 187mg of the title compound as a colorless liquid.

¹H NMR(CDCl₃, ppm) : δ 7.55(s, 1H), 7.40(s, 2H), 3.50(m, 1H), 3.25(m, 2H), 2.85(m, 2H), 2.35-1.85(m, 8H), 1.65(m, 1H)

i) Synthesis of 3-methyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]benzo[b]furan-6-carbonitrile:

185mg of the compound obtained in the above h) was treated according to the same procedure as Example 11-a) to obtain 161mg of the colorless foamy solid product, which was then treated according to the same procedure as Example 1-l) to obtain 100mg of the title compound as a colorless foamy solid.

j) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-cyano-3-methylbenzo[d]-furan-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate:

100mg of the compound obtained in the above i) was treated according to the same procedure as Example 1-m) to obtain 61mg of the title compound as a colorless foamy solid.

¹H NMR(CDCl₃, ppm) : δ 7.65(s, 1H), 7.45(s, 2H), 4.20-4.0(m, 3H), 3.90(m, 1H), 3.50(m, 2H), 3.15(m, 1H), 2.80(m, 3H), 2.15(s, 3H), 2.10-1.60(m, 12H), 1.20(t, 3H, J=7.19Hz)

k) Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-3-methylbenzo[d]-furan-2-yl)ethyl]pyrrolidiny]carbonyl]pyrrolidiny]acetate:

60mg of the compound obtained in the above j) was treated according to the same procedure as Example 1-n) to obtain 2.9mg of the title compound as a colorless foamy solid.

^1H NMR(CDCl_3 , ppm) : δ 7.65(m, 1H), 7.45(m, 2H), 4.80(br, 3H), 4.20-4.0(m, 3H), 3.85(m, 1H), 3.50(m, 4H), 3.15(m, 1H), 2.80(m, 3H), 2.15(s, 3H), 2.10-1.60(m, 10H), 1.20(t, 3H, $J=7.19\text{Hz}$)

ES-MS : 456($\text{M}+2$)⁺

Example 149 : Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]benzo[b]thiophene-5-carboxamide (Compound 253)

a) Synthesis of 5-bromo-2-((dimethylamino)thioxomethoxy)benzaldehyde:

In a 500ml flask, 35.6g of 5-bromosalicyl aldehyde was dissolved in 150ml of acetone, and 29.38g of anhydrous potassium carbonate was added. Thereafter, 21.9g of N,N-dimethylthiocarbamoyl chloride was slowly added, and the reaction solution thereby obtained was then stirred for 2 hours, poured into ice-water and then stirred. The resulting precipitate was filtered and washed three times with water. The filtered solid product was dried and then recrystallized from ethyl acetate/n-hexane(1:3) solvent system to obtain 42.3g of the title compound as a white solid.

^1H NMR(CDCl_3 , ppm) : δ 10.03(s, 1H), 8.01(m, 1H), 7.72(m, 1H), 7.02(m, 1H), 3.47(s, 3H), 3.42(s, 3H)

ES-MS : 311($\text{M}+\text{Na}^+$), 289($\text{M}+1$)⁺

b) Synthesis of N,N-dimethyl(4-bromo-2-formylphenylthio)formamide:

In a 100ml flask, 42.3g of 5-bromo-2-((dimethylamino)thioxomethoxy)benzaldehyde was introduced, melted for 10 minutes in oil bath at

210-220°C and then dissolved in 30ml of toluene. After 100ml of methanol was added, the resulting precipitate was filtered, washed several times with n-hexane and then dried to obtain 12.3g of the title compound as a white solid.

5

¹H-NMR(CDCl₃, ppm) : δ 10.25(s, 1H), 8.13(m, 1H), 7.70(m, 1H), 7.31(m, 1H), 3.15(s, 3H), 3.03(s, 3H)

Mass : 311(M+Na⁺), 289(M+1)⁺

10 c) Synthesis of 1-(5-bromobenzo[b]thiophen-2-yl)ethan-1-one:

In a 100ml flask, 12.3g of N,N-dimethyl(4-bromo-2-formylphenyl-thio)formamide was dissolved in 35ml of methyl orthoformate, and 0.6g of p-toluenesulfonate was added. The reaction solution was stirred for 50
15 minutes at refluxing temperature and then cooled, and saturated NaHCO₃ solution was added. The organic layer was then extracted three times with benzene. After the extract was evaporated to remove the solvent, the residue was dissolved in 60ml of methanol, and 20ml of 2N-NaOH was added thereto. The reaction solution was refluxed under nitrogen
20 atmosphere for one hour, cooled, adjusted to pH 1 with concentrated hydrochloric acid, and then extracted with benzene. After the solvent was removed from the extract, the residue was dissolved in 13ml of acetone. To the resulting solution was slowly added 3.5g of chloroacetone at room temperature. 1.3g of anhydrous potassium
25 carbonate and 90ml of acetone were slowly added thereto. The reaction solution was stirred for 30 minutes at room temperature, refluxed again for 30 minutes, cooled and then filtered to remove the insoluble material. The filtrate was evaporated and then purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions
30 containing the desired product were combined and then evaporated to obtain 1.66g of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 8.03(m, 1H), 7.85(s, 1H), 7.75(m, 1H), 7.54(m, 1H), 2.66(s, 3H)

35

d) Synthesis of 5-bromobenzo[b]thiophene-2-carboxylic acid:

1.25ml of bromine was slowly added to 10ml of 5N aqueous NaOH solution with stirring and the resulting solution was cooled to -5°C-0°C. At the same temperature, a solution of 1.66g of 1-(5-bromobenzo[b]thiophene-2-yl)ethan-1-one in 15ml of 1,4-dioxane was slowly added thereto. The reaction solution was stirred for 30 minutes at room temperature and then for 30 minutes at 50°C, cooled, poured into ice-water and then adjusted to pH 2 with concentrated hydrochloric acid. The resulting precipitate was filtered, washed several times with water, dried and then purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:2)]. The fractions containing the desired product were combined and evaporated to obtain 1.42g of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 8.03(m, 1H), 7.92(s, 1H), 7.76(m, 1H), 7.50(m, 1H)

e) Synthesis of ethyl 5-bromobenzo[b]thiophene-2-carboxylate:

In a 100ml flask, 1.42g of 5-bromobenzo[b]thiophene-2-carboxylic acid and 25ml of methanol were introduced and then stirred. The resulting suspension was cooled in ice bath and 0.6ml of thionyl chloride was slowly added thereto. The reaction solution was refluxed for one hour and then cooled. After 1.1ml of thionyl chloride was added, the reaction solution was refluxed for further 2 hours, cooled and then adjusted to pH 9 with saturated NaHCO₃ solution. The resulting precipitate was filtered, dried and then purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and then evaporated to obtain 1.3g of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 8.01(m, 1H), 7.96(s, 1H), 7.73(m, 1H), 7.54(m, 1H), 4.41(q, 2H, J=7.0Hz), 1.42(t, 3H, J=7.0Hz)

f) Synthesis of ethyl 5-cyanobenzo[b]thiophene-2-carboxylate:

In a 50ml flask, 1.3g of 5-bromobenzo[b]thiophene-2-carboxylate and 1.02g of CuCN were introduced and 20ml of N-methyl-2-pyrrolidone was then added thereto. The mixture was stirred and the resulting suspension was refluxed under nitrogen atmosphere for 2 hours at 200°C.

The reaction solution was cooled, poured into ice-water, vigorously stirred and then filtered to remove the insoluble material. The filtrate was then extracted with ethyl acetate. The extract was evaporated to remove the solvent, and the residue was then purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and evaporated to obtain 330mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 8.21(m, 1H), 8.09(s, 1H), 7.97(m, 1H), 7.70(m, 1H), 4.45(q, 2H, J=7.0Hz), 1.43(t, 3H, J=7.0Hz)

g) Synthesis of 2-(hydroxymethyl)benzo[b]thiophene-5-carbonitrile:

220mg of the compound obtained in the above f) was treated according to the same procedure as Example 1-e) to obtain 120mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 8.03(m, 1H), 7.90(m, 1H), 7.51(m, 1H), 7.26(s, 1H), 4.97(s, 2H)

h) Synthesis of (5-cyanobenzo[b]thiophen-2-yl)methyltriphenylphosphonium bromide:

120mg of the compound obtained in the above g) was treated according to the same procedure as Example 1-f) to obtain 215mg of the title compound as a yellowish white solid.

¹H NMR(CDCl₃, ppm) : δ 8.09-7.27(m, 19H), 6.70(s, 2H)

i) Synthesis of tert-butyl (S)-2-[2-(5-cyanobenzo[b]thiophen-2-yl)vinyl]-

pyrrolidine carboxylate:

211mg of (5-cyanobenzo[b]thiophen-2-yl)methyltriphenylphosphonium bromide obtained in the above h) was reacted according to the same procedure as Example 1-j) to obtain 150mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 8.01(m, 1H), 7.81(m, 1H), 7.48(m, 1H), 7.14(s, 1H), 6.69-6.49(m, 1H), 6.13-6.05(m, 1H), 4.57-4.32(m, 1H), 3.42(m, 2H), 2.38-1.73(m, 4H), 1.48(brs, 9H)

ES-MS : 377(M+Na⁺), 355(M+1)⁺

j) Synthesis of tert-butyl (S)-[2-(5-cyanobenzo[b]thiophen-2-yl)ethyl]-pyrrolidine carboxylate:

155mg of the compound obtained in the above i) was treated according to the same procedure as Example 1-k) to obtain 130mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.93(m, 1H), 7.82(m, 1H), 7.41(m, 1H), 7.08(s, 1H), 3.90(brs, 1H), 3.52-3.27(m, 2H), 2.89(m, 2H), 2.35-1.65(m, 6H), 1.41(brs, 9H)

ES-MS : 379(M+Na⁺), 357(M+1)⁺

k) Synthesis of 2-((S)-2-pyrrolidin-2-ylethyl)benzo[b]thiophene-5-carbonitrile:

128mg of the compound obtained in the above j) was treated according to the same procedure as Example 1-l) to obtain 72mg of the title compound as a white solid.

l) Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]benzo[b]thiophene-5-carbonitrile:

72mg of the compound obtained in the above k) and phenylacetyl chloride were reacted according to the same procedure as Example 1-m)

to obtain 55mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.94(m, 1H), 7.80(m, 1H), 7.43(m, 1H), 7.36-7.23
(m, 5H), 7.11(s, 1H), 4.22(m, 1H), 3.66(m, 2H), 3.48(m, 2H),
2.93(m, 2H), 2.39-1.75(m, 6H)

ES-MS : 397(M+Na⁺), 375(M+1)⁺

m) Synthesis of 2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]- benzo
-[b]thiophene-5-carboxamidine:

55mg of the compound obtained in the above l) was treated
according to the same procedure as Example 1-n) to obtain 45mg of the
title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.91(m, 1H), 7.75(m, 1H), 7.46(m, 1H), 7.32-7.13
(m, 5H), 7.07(s, 1H), 4.23(m, 1H), 3.66-3.58(m, 2H), 3.48(m, 2H),
2.89(m, 2H), 2.38-1.75(m, 6H)

ES-MS : 392(M+1)⁺

IR(KBr) : 3079, 2954, 1613 cm⁻¹

Example 150 : Synthesis of 3-methoxy-2-[2-[(S)-1-(2-phenyl-
acetyl)pyrrolidin-2-yl]ethyl]benzo[b]thiophene-6-carboxamidine
(Compound 255)

a) Synthesis of prop-2-enyl 3-nitro-4-(prop-2-enoxycarbonyl)benzoate:

In a 500ml flask, 25g of 2-nitrobenzene-1,4-dicarboxylic acid and
21.88g of NaHCO₃ were dissolved in 150ml of N,N-dimethylformamide.
To the resulting solution was slowly added 25.6ml of allyl bromide. The
reaction solution was stirred for 3 hours at 50°C, cooled, adjusted to pH 6
with 2N-HCl and then extracted three times with ethyl acetate. The
combined extract was dried and then purified with silica gel column
chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions
containing the desired product were combined and then evaporated to
obtain 34g of the title compound as a pale yellow liquid.

^1H NMR(CDCl_3 , ppm) : δ 8.61(m, 1H), 8.33(m, 1H), 7.82(m, 1H), 6.14-5.94
(m, 2H), 5.49-5.32(m, 4H), 4.92-4.86(m, 4H)
ES-MS : 314(M+Na $^+$)

5 b) Synthesis of methyl 3-hydroxy-6-(prop-2-enyloxycarbonyl)benzo[b]-
thiophene-2-carboxylate:

In a 500ml flask, 34g of the compound obtained in the above a)
and 15.66ml of methyl thioglycolate were dissolved in 150ml of
10 N,N-dimethylformamide. The resulting solution was cooled in ice-bath
and lithium hydroxide was added portionwise thereto. The reaction
solution was stirred for 30 minutes under ice-bath and then for 2 hours
at room temperature, poured into ice-water, treated with concentrated
hydrochloric acid and then extracted three times with ethyl acetate. The
15 combined extract was dried and purified with silica gel column
chromatography [eluent: ethyl acetate/n-hexane(1:7)]. The fractions
containing the desired product were combined and then evaporated to
obtain 13.1g of the title compound as a white solid.

20 ^1H NMR(CDCl_3 , ppm) : δ 10.08(s, 1H), 8.52(s, 1H), 8.09-7.98(m, 2H),
6.12-6.01(m, 1H), 5.49-5.33(m, 2H), 4.89(m, 2H), 3.97(s, 3H)
ES-MS : 315(M+Na $^+$), 293(M+1) $^+$

25 c) Synthesis of 3-hydroxy-2-(methoxycarbonyl)benzo[b]thiophene-6-car-
boxylic acid:

In a 500ml flask, 22.8g of the compound obtained in the above b)
and 32.8g of dimedone were dissolved in 150ml of tetrahydrofuran, and
4.5g of tetrakis(triphenylphosphine)palladium [$\text{Pd}(\text{PPh}_3)_4$] was added
30 thereto. The reaction solution was stirred for 3 hours at room
temperature. The resulting precipitate was filtered, washed several
times with ethyl acetate and then dried in air to obtain 18.2g of the title
compound as a white solid.

35 ^1H NMR($\text{DMSO}-d_6$, ppm) : δ 8.56(s, 1H), 8.01-7.91(m, 2H), 3.87(s, 3H)

d) Synthesis of methyl 6-carbamoyl-3-hydroxybenzo[b]thiophene-2-carboxylate:

In a 100ml flask, 18.2g of the compound obtained in the above c) was dissolved in 40ml of thionyl chloride. The resulting solution was refluxed for 30 minutes, cooled and then distilled under reduced pressure to remove thionyl chloride. The remaining thionyl chloride was removed for 5 hours by means of a vacuum pump. To the dried product was slowly added 40ml of NH_4OH at 0°C . The reaction solution was stirred for 4 hours at room temperature, and the resulting precipitate was filtered, washed several times with ethyl acetate and then dried to obtain 17.5g of the title compound as a white solid.

^1H NMR(DMSO- d_6 , ppm) : δ 8.17(s, 1H), 7.98(brs, 1H), 7.79-7.69(m, 2H), 7.30(brs, 1H), 3.69(s, 3H)

e) Synthesis of methyl 6-cyano-3-hydroxybenzo[b]thiophene-2-carboxylate

In a 500ml flask, 17.5g of the compound obtained in the above d) was dissolved in 50ml of tetrahydrofuran, and a solution of 54.8g of triphenylphosphine in 100ml of carbon tetrachloride was slowly added. The reaction solution was stirred for 30 minutes at room temperature and then for one day at 60°C , cooled and filtered to remove the insoluble material. The filtrate was purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and evaporated to obtain 457mg of the title compound as a pale pink solid.

^1H NMR(CDCl_3 , ppm) : δ 10.14(s, 1H), 8.06-7.99(m, 2H), 7.62(m, 1H), 3.99(s, 3H)

ES-MS : 489($2\text{M}+\text{Na}^+$), 256($\text{M}+\text{Na}^+$)

f) Synthesis of methyl 6-cyano-3-methoxybenzo[b]thiophene-2-carboxylate:

In a 50ml flask, 227mg of the compound obtained in the above e) was dissolved in 10ml of N,N-dimethylformamide, and 47mg of NaH was added thereto at 0°C. To this mixture was slowly added 0.15ml of methyl iodide. The reaction solution was stirred for 4 hours at 60°C and ice-water was then added. This solution was extracted three times with dichloromethane. The extract was dried and purified with silica gel column chromatography [eluent: ethyl acetate/n-hexane(1:3)]. The fractions containing the desired product were combined and evaporated to obtain 153mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 8.08(m, 1H), 7.95(m, 1H), 7.59(m, 1H), 4.22(s, 3H), 3.97(s, 3H)

ES-MS : 270(M+Na⁺)

g) Synthesis of 2-(hydroxymethyl)-3-methoxybenzo[b]thiophene-6-carbonitrile:

260mg of the compound obtained in the above f) was treated according to the same procedure as Example 1-e) to obtain 176mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 8.06(m, 1H), 7.79(m, 1H), 7.58(m, 1H), 4.97(s, 2H), 4.01(s, 3H)

ES-MS : 461(2M+Na⁺), 242(M+Na⁺)

h) Synthesis of (6-cyano-3-methoxybenzo[b]thiophen-2-yl)methyltriphenylphosphonium bromide:

176mg of the compound obtained in the above g) was treated according to the same procedure as Example 1-f) to obtain 340mg of the title compound as a white solid.

¹H NMR(CDCl₃, ppm) : δ 7.91-7.52(m, 18H), 5.89(m, 2H), 3.89(s, 3H)

i) Synthesis of tert-butyl (S)-[2-(6-cyano-3-methoxybenzo[b]thiophen-2-yl)vinyl]pyrrolidine carboxylate:

335mg of (6-cyano-3-methoxybenzo[b]thiophen-2-yl)methyltriphenylphosphonium bromide obtained in the above h) was treated according to the same procedure as Example 1-j) to obtain 230mg of the title compound as a white solid.

5

^1H -NMR(CDCl_3 , ppm) : δ 8.00(m, 1H), 7.76(m, 1H), 7.57(m, 1H), 6.78(m, 1H), 6.10-5.77(m, 1H), 4.96(m, 1H), 3.95(s, 3H), 3.48(m, 2H), 2.38-1.74(m, 4H), 1.42(m, 9H)

10 j) Synthesis of tert-butyl (S)-[2-(6-cyano-3-methoxybenzo[b]thiophen-2-yl)ethyl]pyrrolidine carboxylate:

230mg of the compound obtained in the above i) was treated according to the same procedure as Example 1-k) to obtain 233mg of the title compound as a white solid.

15

^1H NMR(CDCl_3 , ppm) : δ 8.01(m, 1H), 7.72(m, 1H), 7.51(m, 1H), 3.92(s, 3H), 3.57-3.28(m, 3H), 2.86(m, 2H), 2.28-1.66(m, 6H), 1.43(m, 9H)

20 ES-MS : 409(M+Na $^+$)

k) Synthesis of 3-methoxy-2-[(S)-2-pyrrolidin-2-yl)ethyl]benzo[b]thiophene-6-carbonitrile:

25 230mg of the compound obtained in the above j) was treated according to the same procedure as Example 1-l) to obtain 39mg of the title compound as a colorless oil.

^1H NMR(CDCl_3 , ppm) : δ 7.97(m, 1H), 7.71(m, 1H), 7.55(m, 1H), 3.90(s, 3H), 3.58(m, 1H), 3.47-3.29(m, 2H), 3.08(m, 2H), 2.50-1.80(m, 6H)

30

ES-MS : 287(M+1) $^+$

l) Synthesis of 3-methoxy-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl)-ethyl]benzo[b]thiophene-6-carbonitrile:

35

39mg of the compound obtained in the above k) and phenylacetyl chloride were reacted according to the same procedure as Example 1-m) to obtain 18mg of the title compound as a colorless oil.

- 5 ¹H NMR(CDCl₃, ppm) : δ 7.98(m, 1H), 7.68(m, 1H), 7.48(m, 1H), 7.23(m, 5H), 4.24(m, 1H), 3.89(s, 3H), 3.65(m, 2H), 3.47(m, 2H), 2.88(m, 2H), 2.32-1.65(m, 6H)
ES-MS : 427(M+Na⁺), 405(M+1)⁺

- 10 m) Synthesis of 3-methoxy-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]-ethyl]benzo[b]thiophene-6-carboxamide:

18mg of the compound obtained in the above l) was treated according to the same procedure as Example 1-n) to obtain 10mg of the
15 title compound as a pale yellow solid.

- ¹H NMR(CDCl₃) : δ 7.97(m, 1H), 7.68-7.52(m, 2H), 7.26-6.98(m, 5H), 4.16(m, 1H), 3.87(s, 3H), 3.65(m, 2H), 3.44(m, 2H), 2.87(m, 2H), 2.26-1.58(m, 6H)
20 ES-MS : 422(M+1)⁺
IR(KBr) : 2992, 1612, 1460 cm⁻¹

- Example 151 : Synthesis of N-methyl [3-[[[(S)-2-[2-[6-[imino-(methylamino)methyl]-1-methylindol-2-yl]ethyl]pyrrolidinyl]methyl]-benzo[b]thiophen-2-yl]formamide (Compound 258)
25

68mg of 1-methyl-2-[2-[(S)-1-[[2-(N-methylcarbamoyl)benzo[b]thiophene-3-yl]methyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide obtained in Example 10 was dissolved in 10ml of 40% methylamine methanol solution and then stirred overnight at room temperature. The
30 reaction solution was distilled under reduced pressure to remove the reaction solvent and the residue was purified with column chromatography [eluent: dichloromethane/methanol(10:1)] on NH-DM1020 silica. The fractions containing the desired product were combined and distilled
35 under reduced pressure to obtain 52mg of the title compound as a pale

yellow solid.

¹H NMR(MeOH-d₄, ppm) : δ 7.91(d, 1H), 7.84(d, 1H, J=6.54Hz), 7.67(s, 1H), 7.52(d, 1H), 7.39-7.31(m, 3H), 6.15(s, 1H), 4.12(d, 1H),
5 3.83(d, 1H), 3.62(s, 3H), 3.05(s, 3H), 2.99(s, 1H), 2.85(m, 1H),
2.77-2.70(m, 2H), 2.41(m, 1H), 2.19(m, 1H), 2.05(m, 1H),
1.79-1.58(m, 4H)

10 Example 152 : Synthesis of 1-[(S)-2-[2-(6-[(hydroxyimino)amino-methyl]-1-ethylindol-2-yl)ethylpyrrolidinyl]-2-phenylethan-1-one
(Compound 260)

190mg of 1-ethyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]-ethyl]indole-6-carbonitrile obtained in Example 14-a) was dissolved in
15 methanol. 103mg of hydroxylamine hydrochloride and 210mg of sodium carbonate were added and the reaction solution was refluxed overnight with stirring. After water was added, the reaction solution was extracted two times with dichloromethane. The extract was dried over MgSO₄ and distilled under reduced pressure. The residue was purified
20 with silica gel column chromatography [eluent: dichloromethane/methanol (20:1)] to obtain 11mg of the title compound.

¹H NMR(MeOH-d₄) : δ 7.52(s, 1H), 7.34(d, 1H, J=8.38Hz), 7.27-6.80(m, 6H), 6.18(s, 1H), 4.08(m, 3H), 3.60(d, 2H, J=5.36Hz), 3.44(m, 2H),
25 2.66(t, 2H, J=8.00Hz), 2.13(m, 1H), 1.92-1.60(m, 6H), 1.21(t, 3H, J=7.15Hz)

ES-MS : 419(M+1)⁺, 441(M+Na)

30 Example 153 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-[6-[(hydroxyimino)aminomethyl]-1-ethylindol-2-yl)ethylpyrrolidinyl]carbonylpyrrolidinyl]acetate (Compound 261)

480mg of ethyl 2-[(R)-2-[(S)-2-[2-(6-cyano-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonylpyrrolidinyl]acetate obtained in Example 60-a)
35 was dissolved in methanol. 304mg of hydroxylamine hydrochloride and

695mg of sodium carbonate were added and the reaction solution was refluxed overnight with stirring. After water was added, the reaction solution was extracted two times with dichloromethane. The extract was dried over MgSO_4 and distilled under reduced pressure. The residue was purified with silica gel column chromatography [eluent: dichloromethane/methanol(20:1)] to obtain 27mg of the title compound.

^1H NMR($\text{MeOH}-d_4$, ppm) : δ 7.53(s, 1H), 7.35(d, 1H, $J=8.25\text{Hz}$), 7.21(d, 1H, $J=4.43\text{Hz}$), 6.21(s, 1H), 4.11(m, 3H), 3.99(m, 2H), 3.68(t, 1H), 3.49(m, 2H), 3.34(d, 2H, $J=18.9\text{Hz}$), 3.12(m, 1H), 2.68(m, 2H), 2.25-1.60(m, 11H), 1.25(t, 3H), 1.10(t, 3H)

ES-MS : 482(M+1) $^+$

Example 154 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-[1-ethyl-6-[(acetylamino)iminomethyl]indol-2-yl]ethyl]pyrrolidinyl]carbonyl]-pyrrolidinyl]acetate (Compound 265)

52mg of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 60 was dissolved in dry dichloromethane. To the resulting solution was added 31 μl of triethylamine, and the mixture was cooled to -78°C . After 16 μl of acetyl chloride was added, the reaction solution was stirred for 3 hours and warmed to room temperature. Water was added and the mixture was extracted with dichloromethane. The extract was dried over MgSO_4 and evaporated under reduced pressure to remove the solvent. The residue was purified with silica gel column chromatography [eluent: ethyl acetate/methanol(50:1)] to obtain 7mg of the title compound as a pale yellow solid.

^1H NMR($\text{MeOH}-d_4$, ppm) : δ 7.72(s, 1H), 7.44(d, 1H, $J=8.00\text{Hz}$), 7.29(d, 1H, $J=8.27\text{Hz}$), 6.28(s, 1H), 4.17(m, 3H), 4.02(m, 2H), 3.70(m, 1H), 3.49(m, 4H), 3.33(d, 2H, $J=20.26\text{Hz}$), 3.09(m, 1H), 2.75(m, 2H), 2.64(m, 1H), 2.30-1.60(m, 8H), 1.25(t, 3H), 1.19(s, 3H), 1.07(t, 3H)

Example 155 : Synthesis of N-[[1-ethyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]indol-6-yl]iminomethyl]ethoxyformamide (Compound 266)

5 170mg of 1-ethyl-2-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]-ethyl]indole-6-carboxamide obtained in Example 14 was dissolved in dichloromethane. 90 μ l of triethylamine and 70mg of ethyl chloroformate were added at 0 $^{\circ}$ C. The reaction solution was stirred for one hour at room temperature and distilled under reduced pressure to remove the
10 reaction solvent. The residue was purified with column chromatography [eluent: ethyl acetate] on NH-DM1020 silica. The fractions containing the desired product were combined and distilled under reduced pressure to obtain 110mg of the title compound as a white solid.

15 ^1H NMR(MeOH- d_4 , ppm) : δ 8.34(s, 1H), 7.49(d, 1H), 7.42(m, 1H), 7.38-7.22(m, 5H), 6.36(s, 1H), 4.34-4.22(m, 6H), 3.66(s, 2H), 3.50(m, 3H), 2.77(m, 2H), 2.33(m, 1H), 1.98(m, 5H), 1.74(m, 3H), 1.37(m, 6H)

20 Example 156 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-[1-ethyl-6-[(ethoxycarbonylamino)iminomethyl]indol-2-yl]ethyl]pyrrolidinyl]-carbonyl]pyrrolidinyl]acetate (Compound 267)

25 200mg of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 60 was dissolved in dichloromethane and then cooled to 0 $^{\circ}$ C. 119 μ l of triethylamine was added and after 30 minutes, 49 μ l of ethyl chlorocarbonate was added. After one hour, water was added to the reaction solution, which was then extracted two times with dichloromethane.
30 The combined extract was dried over MgSO_4 and then concentrated. The residue was subjected to column chromatography [eluent: ethyl acetate] on NH-DM1020 silica to obtain 124mg of the title compound.

35 ^1H NMR(MeOH- d_4 , ppm) : δ 8.03(s, 1H), 7.20(s, 1H), 6.40(s, 1H), 4.35-4.05(m, 7H), 3.81(q, 1H), 3.74-3.34(m, 4H), 3.25(m, 1H), 2.85(m,

2H), 2.77(m, 1H), 2.40-1.70(m, 10H), 1.35(m, 6H), 1.22(m, 3H)

Example 157 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-[1-ethyl-6-[[iminol(methylethoxy)carbonylamino]methyl]indol-2-yl]ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 270)

200mg of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 60 was reacted with 67 μ l of isobutylchloroformate according to the same procedure as Example 154 to obtain 195mg of the title compound.

¹H NMR(MeOH-d₄, ppm) : δ 7.91(s, 1H), 7.42(m, 2H), 6.32(s, 1H), 4.18(m, 3H), 3.75(d, 2H, J=6.66Hz), 3.67(t, 1H), 3.50(m, 3H), 3.30(d, 2H), 3.08(m, 1H), 2.74(m, 2H), 2.62(q, 1H), 2.30-1.60(m, 12H), 1.28(t, 3H), 1.08(t, 3H), 0.92(d, 6H)

Example 158 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-[6-[[trichloromethoxy]carbonylamino]iminomethyl]-1-ethylindol-2-yl]ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 272)

100mg of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 60 was reacted with 35 μ l of trichloroethylchloroformate treated according to the same procedure as Example 154 to obtain 92mg of the title compound.

¹H NMR(MeOH-d₄, ppm) : δ 7.97(s, 1H), 7.46(m, 2H), 6.29(s, 1H), 4.81(s, 2H), 4.18(m, 3H), 3.67(t, 1H), 3.57-3.05(m, 7H), 2.76(m, 2H), 2.64(q, 1H), 2.30-1.60(m, 10H), 1.27(t, 3H), 1.07(t, 3H)

Example 159 : Synthesis of ethyl 2-[(R)-2-[(S)-2-[2-[1-ethyl-6-[[imino(phenylcarbonylamino)methyl]indol-2-yl]ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate (Compound 273)

60mg of ethyl 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)-ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate obtained in Example 60 was

reacted with 24 μ l of benzylchloroformate according to the same procedure as Example 154 to obtain 64mg of the title compound.

¹H NMR(MeOH-d₄, ppm) : δ 8.10-6.60(m, 8H), 6.30(s, 1H), 4.16(m, 3H),
4.00(m, 2H), 3.65(m, 1H), 3.49(m, 2H), 3.34(d, 2H, J= 19.08Hz),
3.11(m, 1H), 2.75(m, 2H), 2.66(q, 1H), 2.40-1.60(m, 10H), 1.26(t,
3H), 1.11(t, 3H)

ES-MS : 588(M+1)⁺

10 Test 1 : Inhibitory activity for thrombin and trypsin

20 μ l of each compound of the present invention was dissolved in 50% methanol in various concentrations and then added to each well of a microplate, to each of which 160 μ l of the reaction medium containing
15 125mM NaCl, 50mM Tris-HCl (pH 8.0) and 2mM synthetic substrate (N-benzoyl-Phe-Val-Arg-p-nitroanilide, Sigma B-7632) were added. 20
 μ l of human thrombin solution (5 units/ml, Sigma T-6759, manufactured by Sigma Co.) containing 0.1% bovine serum albumin was added to each
well to initiate the enzymatic reaction. After 20 minutes, the hydrolysis
20 of substrate was determined by measuring the absorbance at 405nm. The concentration of the test compound showing half the change of the
absorbance in the well that did not contain the test compound was represented as IC₅₀ value. The selectivity index was calculated by
dividing the IC₅₀ value for trypsin by the IC₅₀ value for thrombin. The
25 thrombin inhibitory activity and the trypsin inhibitory activity for the
compound of the present invention are shown in the following Table 2.

Table 2. Inhibitory activity for thrombin and trypsin

Compound No.	Inhibitory activity (IC ₅₀)		Selectivity (trypsin/thrombin)
	Thrombin(nM)	Trypsin(nM)	
8	9.47	460.0	48.6
9	33.9		
15	20.1	608.0	30.2
24	8.45	706.0	83.6
30	9.01	420.0	46.6
37	5.40		
38	7.59	184.0	24.2
39	6.91		
40	7.95		
43	9.96	401.0	40.3
44	9.23	313.0	33.9
46	28.9		
57	7.73		
58	3.00	52.2	17.4
62	11.7	582.0	49.7
64	15.2	349.0	22.9
65	22.1		
72	9.4	128.0	13.6
73	33.2	268.0	
83	30.9		
84	51.6	4490.0	87.0
86	27.0	674.0	25.0
88	15.9	128.0	8.1

Table 2. (continued)

Compound No.	Inhibitory activity (IC ₅₀)		Selectivity (trypsin/thrombin)
	Thrombin(nM)	Trypsin(nM)	
98	20.3		
109	31.9		
110	37.7	1460.0	38.6
112	29.2		
114	17.4	500.0	28.8
115	31.8		
116	31.7	869.0	27.4
117	16.7	811.0	48.6
118	12.3	178.0	14.5
123	32.9		
125	22.3	775.0	34.7
126	40.5		
127	21.7		
128	26.2		
129	13.1	139.0	10.6
130	36.5		
131	9.29	137.0	14.7
142	33.1		
143	5.46	410.0	75.2
144	25.3		
145	26.1	524.0	20.1
146	22.1	464.0	21.0
147	25.5		

Table 2. (continued)

Compound No.	Inhibitory activity (IC ₅₀)		Selectivity (trypsin/thrombin)
	Thrombin(nM)	Trypsin(nM)	
148	23.0	443.0	19.2
149	10.4		
155	11.6	287.0	24.7
156	28.6		
157	26.9		
158	5.50		
159	19.3	399.0	20.7
160	15.3	382.0	25.0
161	5.21	255.0	48.9
162	7.3	329.0	45.0
163	19.4	497.0	25.6
166	33.1	617.0	18.6
167	18.3	322.0	17.6
168	31.6		
169	30.2		
170	33.5	1070.0	31.9
171	10.6	373.0	35.1
173	34.6		
174	16.2	416.0	25.7
175	9.92		
176	21.7	450.0	20.7
177	18.8	500.0	26.6
180	11.0	351.0	31.8

Table 2. (continued)

Compound No.	Inhibitory activity (IC ₅₀)		Selectivity (trypsin/thrombin)
	Thrombin(nM)	Trypsin(nM)	
182	10.1	304.0	30.0
184	9.51	551.0	57.9
187	25.6		
192	33.8		
194	31.7		
196	37.2	536.0	14.4
222	11.4		
224	24.1		
244	53.6		

Test 2 : Measurement of the thrombin time (TT) in rat plasma

SD male rats weighing 220 ± 20 g which had fasted overnight were used as experimental animals. Blood taken from the hearts of the experimental animals just before administration of the test compound and at 30, 60, 120 and 240 minutes after oral administration of the test compound was mixed with 0.108M sodium citrate in the ratio of 9:1. The mixtures thereby obtained were centrifuged at 15,000rpm for 5 minutes at 4°C to separate the plasma, which was stored at -20°C until the TT was measured by means of the method described below.

200 μ l of Owren's buffer was added to 50 μ l of the plasma and 100 μ l of the diluted plasma thereby obtained was injected into the vial of a coagulometer and then incubated for 2 minutes at 37°C. To each vial was added 100 μ l of thrombin at a concentration of 20U/ml, which had prewarmed at 37°C, to measure the time (TT) until clotting occurred.

The ratio of the TT in rat plasma after administration of the test compound to the TT in rat plasma before administration of the test compound was calculated. The TT ratios for the compounds of the present invention are shown in the following Table 3.

5

Table 3. Plasma TT ratio after administration to rat

Compound No.	Dosage		
	30mg/kg	50mg/kg	100mg/kg
86	1.49	4.51	5.19
88	2.62	7.83	
118		8.80	
126		5.40	
127		8.00	
149		9.24	
155		3.93	7.36
159		6.23	
160		2.30	
161		7.62	
171			4.23
267		4.48	
270	1.46	4.30	
272	1.76	2.84	

30 Test 3 : Pharmacokinetic test

Test method :

35 S.D. male rats weighing 200 ± 20 g which had fasted overnight were subjected to cannulation at their femoral veins and arteries.

Compound 88 prepared in Example 62 was dissolved in physiological saline and then administered to the rats both by intravenous injection and oral administration. Blood was taken at prescribed intervals of time and then immediately mixed with methanol. The mixture was centrifuged (15,000rpm, 5 min., 4°C) to obtain quantitative amount of the supernatant which was then subjected to HPLC in Diode Array Detector at 254nm to analyse the concentration of the test compound in the blood.

Test results :

The blood concentrations of compound 88 according to the present invention analysed after intravenous injection and oral administration are shown in the following Tables 4 and 5, and the pharmacokinetic parameter is described in the following Table 6. As can be seen from the experimental results shown in these tables, when compound 88 of the present invention was administered via intravenous injection, it was rapidly distributed in the body and slowly disappeared. In rats, compound 88 of the present invention exhibited a good result, i.e. an elimination half-time of 64 minutes and a bioavailability of 32.6%.

Table 4. Blood concentration of the compound 88 of example 62 following intravenous injection of 10mg/kg in rats

[illegible]

Table 5. Blood concentration of the compound 88 of example 62 following oral administration of 100mg/kg in rats

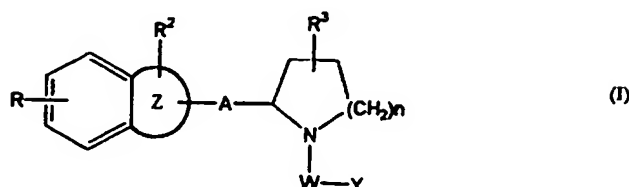
[illegible]

Table 6. Pharmacokinetic parameters of the compound 88 of Example 62 in rats

Parameter	Mean \pm error
Elimination Half-life (hr)	1.07 \pm 0.27
Bioavailability (%)	32.62 \pm 7.69

WHAT IS CLAIMED IS :

1. A compound represented by formula (I):



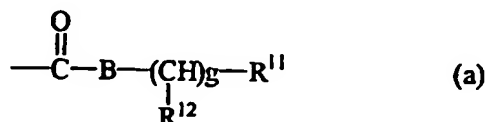
10 and pharmaceutically acceptable salts thereof, in which

R represents a group of formula

or

, wherein

15 R^1 represents hydrogen, hydroxy, alkyl, alkoxy, alkylcarbonyl, alkylcarbonyloxy, aralkoxycarbonyl, or a radical of formula (a),



20 wherein

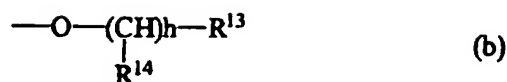
B represents oxygen or sulfur;

25 R^{11} and R^{12} independently of one another represent hydrogen, haloalkyl, alkylcarbonyloxy, dialkylamino, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring; and

g denotes an integer of 0 to 3;

30 R^2 represents hydrogen, hydroxy, halogen, carboxy, aminocarbonyl, alkyl, alkoxy, hydroxyalkyl, aminoalkyl, alkylcarbonyl, alkylsulfonyl, carboxyalkyl, aminocarbonylalkyl, alkoxycarbonylalkyl, or substituted or unsubstituted arylsulfonyl;

R^3 represents hydrogen, halogen, alkyl, hydroxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, carboxy, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, or a radical of formula (b),

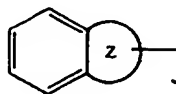


wherein

R¹³ and R¹⁴ independently of one another represent hydrogen, alkyl, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring; and

h denotes an integer of 0 to 3;

the group of formula

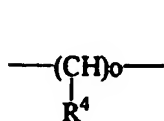


represents a radical selected from

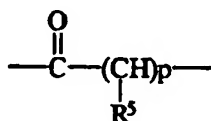
the group consisting of indolyl, benzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, naphthyl, tetrahydronaphthyl, indanyl, dihydrobenzofuranyl and dihydrobenzothienyl;

A represents a saturated or unsaturated alkylene group having 2 to 4 carbon atoms, which may have 1 or 2 substituents selected from the group consisting of carboxy, alkyl, hydroxyalkyl, carboxyalkyl, alkyl-carbonyl, alkoxycarbonyl and alkoxycarbonylalkyl;

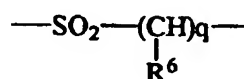
W represents a group of formula (c), (d) or (e),



(c)



(d)

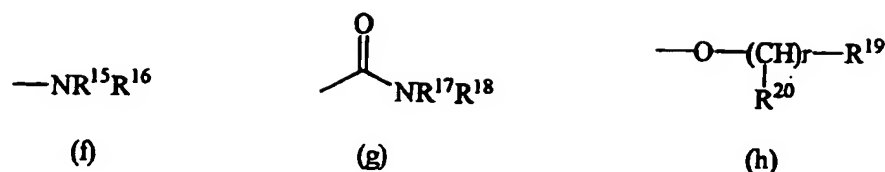


(e)

wherein

o, p and q independently of one another denote an integer of 0 to 3,

R⁴, R⁵ and R⁶ independently of one another represent hydrogen, hydroxy, carboxy, alkoxycarbonyl, substituted or unsubstituted arylsulfonyl, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring, or represents a group of formula (f), (g) or (h),



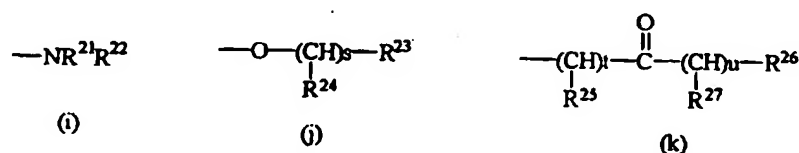
wherein

R^{15} , R^{16} , R^{17} and R^{18} independently of one another represent hydrogen, alkyl, alkylsulfonyl, carboxyalkyl, alkylcarbonyl, aminocarbonylalkyl, alkoxycarbonylalkyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring;

R^{19} and R^{20} independently of one another represent hydrogen, carboxy, aminocarbonyl or alkoxycarbonyl, or represents 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings; and

r denotes an integer of 0 to 3;

Y represents hydrogen or a 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings and which may be substituted on any atom of the ring with a substituent selected from the group consisting of oxygen, halogen, nitro, alkyl, haloalkyl, hydroxyalkyl, alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring, and a group of formula (i), (j) and (k),



wherein

R^{21} and R^{22} independently of one another represent hydrogen, alkyl, alkylsulfonyl, carboxyalkyl, alkylcarbonyl, alkoxycarbonylalkyl, or substituted or unsubstituted arylsulfonyl;

R^{23} and R^{24} independently of one another represent hydrogen, carboxy, aminocarbonyl, alkoxycarbonyl, or 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with one or more 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic rings;

R^{25} , R^{26} and R^{27} independently of one another represent hydrogen, hydroxy, thio, amino, carboxy, aminocarbonyl, alkoxy, alkoxycarbonyl, alkylamino, alkylsulfonylamino, alkenyl, alkoxycarbonylamino, cycloalkylamino, alkoxycarbonylalkylamino, substituted or unsubstituted arylsulfonylamino, or substituted or unsubstituted 3- to 7-membered saturated or unsaturated heterocyclic or carbocyclic ring;

s denotes an integer of 0 to 3;

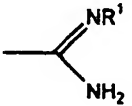
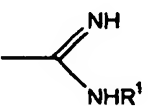
t denotes an integer of 0 to 6; and

u denotes an integer of 0 to 8; and

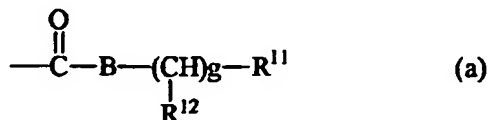
n denotes an integer of 0 to 2,

provided that when each of g, h, o, p, q, r, s, t and u denotes number of 3 or more, the corresponding alkylene chain may be straight or branched.

2. The compound as defined in claim 1, wherein

R represents a group of formula  or , wherein

R^1 represents hydrogen, hydroxy, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_2 - C_4 alkylcarbonyl, C_2 - C_4 alkylcarbonyloxy, or a radical of formula (a),



wherein

B represents oxygen or sulfur,

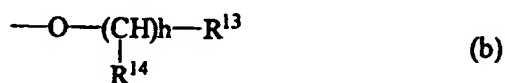
R^{11} and R^{12} independently of one another represents hydrogen, C_1 - C_4

haloalkyl, C₂-C₄ alkylcarbonyloxy, C₂-C₆ dialkylamino, or substituted or unsubstituted 6-membered carbocyclic ring, and

g denotes an integer of 0 to 3;

R² represents hydrogen, halogen, carboxy, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ hydroxyalkyl, C₁-C₄ aminoalkyl, C₂-C₄ alkylcarbonyl, C₁-C₄ alkylsulfonyl, C₂-C₄ carboxyalkyl, C₂-C₄ aminocarbonylalkyl or C₃-C₇ alkoxy-carbonylalkyl;

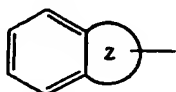
R³ represents hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ hydroxyalkyl, C₂-C₄ carboxyalkyl, C₃-C₇ alkoxy-carbonylalkyl, or a radical of formula (b),



wherein

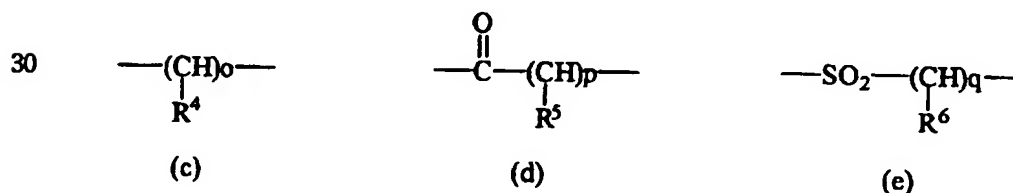
R¹³ and R¹⁴ independently of one another represent hydrogen or phenyl, and

h denotes an integer of 0 to 1;

the group of formula  represents a radical selected from the group consisting of indolyl, benzofuranyl, benzothienyl, benzoimidazolyl and naphthyl;

A represents saturated or unsaturated alkylene group having 2 to 4 carbon atoms, which may have 1 or 2 substituents selected from the group consisting of carboxy, C₁-C₄ hydroxyalkyl and C₂-C₄ alkoxy-carbonyl;

W represents a group of formula (c), (d) or (e),



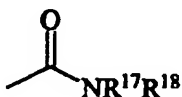
wherein

o, p and q independently of one another denote an integer of 0 to 3,

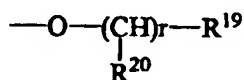
R^4 , R^5 and R^6 independently of one another represent hydrogen, hydroxy, carboxy, C_2 - C_4 alkoxy carbonyl, phenylsulfonyl, or substituted or unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring, or represents a group of formula (f), (g) or (h),



(f)



(g)



(h)

wherein

R^{15} , R^{16} , R^{17} and R^{18} independently of one another represent hydrogen, C_1 - C_4 alkyl, C_1 - C_4 alkylsulfonyl, C_2 - C_4 carboxyalkyl, C_2 - C_4 alkyl-carbonyl, C_2 - C_4 aminocarbonylalkyl, C_3 - C_7 alkoxy carbonylalkyl, or substituted or unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring,

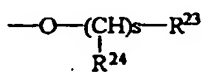
R^{19} and R^{20} independently of one another represent hydrogen, carboxy, aminocarbonyl or C_2 - C_4 alkoxy carbonyl, or represents 5- to 6-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with other one or more 5- to 6-membered saturated or unsaturated heterocyclic or carbocyclic ring, and

r denotes an integer of 0 to 3;

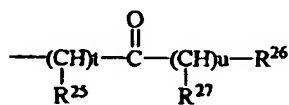
Y represents hydrogen, or represents 5- to 6-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with other one or more 5- to 6-membered saturated or unsaturated heterocyclic or carbocyclic ring and which can be substituted on any atom of the ring with substituent selected from the group consisting of oxygen, halogen, nitro, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 hydroxyalkyl, C_1 - C_4 alkylsulfonyl, phenylsulfonyl, substituted or unsubstituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring, and a group of formula (i), (j) and (k),



(i)



(j)



(k)

wherein

R^{21} and R^{22} independently of one another represent hydrogen, C_1 - C_4 alkyl, C_1 - C_4 alkylsulfonyl, C_2 - C_5 carboxyalkyl, C_2 - C_5 alkylcarbonyl, C_3 - C_7 alkoxyalkyl or phenylsulfonyl,

5 R^{23} and R^{24} independently of one another represent hydrogen, carboxy, aminocarbonyl, C_2 - C_4 alkoxyalkyl, or 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring which may be fused with other one or more 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring,

10 R^{25} , R^{26} and R^{27} independently of one another represents hydrogen, hydroxy, thio, amino, carboxy, aminocarbonyl, C_1 - C_4 alkoxy, C_2 - C_4 alkoxyalkyl, C_1 - C_4 alkylamino, C_1 - C_4 alkylsulfonylamino, C_2 - C_5 alkenyl, C_2 - C_4 alkoxyalkylamino, C_3 - C_6 alkoxyalkylalkylamino, C_3 - C_6 cycloalkylamino, phenylsulfonylamino, or substituted or unsub-
15 stituted 3- to 5-membered saturated or unsaturated heterocyclic or carbocyclic ring,

s denotes an integer of 0 to 3,

t denotes an integer of 0 to 6, and

u denotes an integer of 0 to 8, and

20 n denotes an integer of 0 to 2,

provided that when each of g, h, o, p, q, r, s, t and u denotes number of 3 or more, the corresponding alkylene chain may be straight or branched.

25 3. The compound as defined in claim 1, which is selected from the group consisting of:

3-[[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]-benzo[b]thiophene-2-carboxamide,

30 3-[[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidin-2-yl]methyl]-benzo[b]thiophene-2-carboxamide,

1-ethyl-2-[2-[(S)-1-[2-(3-chlorophenyl)acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide,

2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]benzoic acid,

35 1-ethyl-2-[2-[(S)-1-(2-cyclopentyl-2-phenylacetyl)pyrrolidin-2-yl]ethyl]-

- indole-6-carboxamide,
1-ethyl-2-[2-[(S)-1-((R)-2-methylsulfonylamino-2-phenylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
ethyl 2-[[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenyl]ethyl]amino]acetate,
5 1-ethyl-2-[2-[(S)-1-[(R)-2-(carbamoylmethylamino)-2-phenylacetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
2-[[[(R)-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxo-1-phenylethyl]amino]acetic acid,
10 1-ethyl-2-[2-[(S)-1-(2-cyclopentylacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
ethyl 3-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-cyclopentyl-3-oxopropanoate,
1-ethyl-2-[2-[(S)-1-(2-cyclohexylacetyl)pyrrolidin-2-yl]ethyl]indole-6-
15 carboxamide,
1-ethyl-2-[2-[(S)-1-(2-cyclopropylaminoacetyl)pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
1-ethyl-2-[2-[(S)-1-[2-[cyclopropyl(methylsulfonyl)amino]acetyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
20 ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]cyclopropylamino]acetate,
ethyl 2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetate,
2-[[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-1-methyl-2-oxoethyl]cyclopropylamino]acetic acid,
25 ethyl 4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-cyclopropylamino-4-oxobutanoate,
4-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-3-cyclopropylamino-4-oxobutanoic acid,
30 1-ethyl-2-[2-[(S)-1-((R)-pyrrolidin-2-ylcarbonyl)pyrrolidin-2-yl]ethyl]-indole-6-carboxamide,
ethyl 2-[(R)-2-[[[(S)-2-[2-(6-amidino-1-methylindol-2-yl)ethyl]pyrrolidinyl]carbonyl]pyrrolidinyl]acetate,
ethyl 2-[(R)-2-[[[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-35 -carbonyl]pyrrolidinyl]acetate,

- 2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
-nyl]pyrrolidinyl]acetic acid,
2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]-(S)-4-methyl-
pyrrolidinyl]carbonyl]pyrrolidinyl]acetic acid,
5 ethyl-2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
-carbonyl]pyrrolidinyl]propionate,
ethyl-2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
-carbonyl]pyrrolidinyl]butanoate,
ethyl-2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
10 -carbonyl]pyrrolidinyl]-2-phenylacetate,
1-ethyl-2-[2-[(S)-1-[(R)-1-(carbamoylmethyl)pyrrolidin-2-yl]carbonyl]-
pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
1-ethyl-2-[2-[(S)-1-[(R)-1-[(N-cyclopropylcarbamoyl)methyl]pyrrolidin-2-
-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
15 ethyl (S)-2-[2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyr-
rolidinyl]carbonyl]pyrrolidinyl]acetylamino]propanoate,
1-ethyl-2-[2-[(S)-1-[(R)-1-(1-carbamoyl-3-hydroxypropyl)pyrrolidin-2-
yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
2-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]car-
20 bonyl]pyrrolidinyl]-4-hydroxybutanoic acid,
1-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]car-
bonyl]pyrrolidinyl]ethane-1,2-dicarboxylic acid,
1-ethyl-2-[2-[(S)-1-[[1-(2-oxo-3-oxolanyl)pyrrolidin-2-yl]carbonyl]pyrro-
-lidin-2-yl]ethyl]indole-6-carboxamidine,
25 ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
-carbonyl]pyrrolidinyl]butanoate,
4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
-nyl]pyrrolidinyl]butanoic acid,
ethyl 5-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
30 -carbonyl]pyrrolidinyl]pentanoate,
5-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
-nyl]pyrrolidinyl]pentanoic acid,
ethyl 6-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
-carbonyl]pyrrolidinyl]hexanoate,
35 6-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo

- nyl]pyrrolidinyl]hexanoic acid,
 1-ethyl-2-[2-[(S)-1-[(R)-1-[2-(methylamino)acetyl]pyrrolidin-2-yl]carbo-
 -nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 1-ethyl-2-[2-[(S)-1-[(R)-1-((S)-2-aminopropanoyl)pyrrolidin-2-yl]carbo-
 5 -nyl]-pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 1-ethyl-2-[2-[(S)-1-[(R)-1-(2-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-
 pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 1-ethyl-2-[2-[(S)-1-[(R)-1-((S)-2-amino-3-methylbutanoyl)pyrrolidin-2-
 -yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 10 1-ethyl-2-[2-[(S)-1-[(R)-1-[(S)-2-(methanesulfonylamino)propanoyl]pyr-
 rolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
 -carbonyl]pyrrolidinyl)-(S)-3-amino-4-oxobutanoate,
 1-ethyl-2-[2-[(S)-1-[(R)-1-((S)-2-amino-3-carbamoylpropanoyl)pyrroli-
 15 din-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
 -nyl]pyrrolidinyl)-(S)-3-amino-4-oxobutanoic acid,
 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-aminopropanoyl)pyrrolidin-2-yl]carbonyl]
 -pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 20 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-amino-2-methylpropanoyl)pyrrolidin-2-yl]
 -carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 1-ethyl-2-[2-[(S)-1-[(R)-1-(3-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-
 pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 1-ethyl-2-[2-[(S)-1-[(R)-1-[3-[(methanesulfonyl)amino]propanoyl]pyrro-
 25 lidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
 -carbonyl]pyrrolidinyl)-(S)-2-amino-4-oxobutanoate,
 1-ethyl-2-[2-[(S)-1-[(R)-1-((S)-3-amino-3-carbamoylpropanoyl)pyrroli-
 din-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamidine,
 30 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
 -nyl]pyrrolidinyl)-(S)-2-amino-4-oxobutanoic acid,
 1-ethyl-2-[2-[(S)-1-[[1-[(R)-1-[3-carbamoyl-(S)-3-[(methanesulfonyl)-
 amino]propanoyl]pyrrolidin-2-yl]carbonyl]pyrrolidin-2-yl]ethyl]indole-6-
 carboxamidine,
 35 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo

- nyl]pyrrolidinyl)-(S)-2-[(methanesulfonyl)amino]-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-[(R)-1-(4-aminobutanoyl)pyrrolidin-2-yl]carbonyl]-
pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
1-ethyl-2-[2-[(S)-1-[(R)-1-[(2-piperidiny]carbonyl)pyrrolidin-2-yl]carbo-
5 -nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
1-ethyl-2-[2-[(S)-1-[(R)-1-(3-piperidiny]carbonyl)pyrrolidin-2-yl]carbo-
nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
1-ethyl-2-[2-[(S)-1-[(R)-1-[(4-piperidiny]carbonyl)pyrrolidin-2-yl]carbo-
-nyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
10 1-methyl-2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-
yl]ethyl]indole-6-carboxamide,
1-ethyl-2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl]carbonyl]pyrrolidin-2-
yl]ethyl]indole-6-carboxamide,
1-ethyl-2-[2-[(S)-1-[(R)-1-(2-propylpentanoyl)pyrrolidin-2-yl]carbonyl]
15 -pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
ethyl 3-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
-carbonyl]pyrrolidinyl]-3-oxo-propanoate,
1-ethyl-2-[2-[(S)-1-[(R)-1-(2-carbamoylacetyl)pyrrolidin-2-yl]carbonyl]
-pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
20 ethyl 4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]
-carbonyl]pyrrolidinyl]-4-oxobutanoate,
4-[(R)-2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]carbo-
-nyl]pyrrolidinyl]-4-oxobutanoic acid,
1-ethyl-2-[2-[(S)-1-[(R)-1-(3-hydroxybutanoyl)pyrrolidin-2-yl]carbonyl]
25 -pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
1-ethyl-2-[2-[(S)-1-[(R)-1-prop-2-enoylpyrrolidin-2-yl]carbonyl]pyrro-
lidin-2-yl]ethyl]indole-6-carboxamide,
1-ethyl-2-[2-[(S)-1-[(R)-1-(methanesulfonyl)pyrrolidin-2-yl]carbonyl]-
pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
30 1-ethyl-2-[2-[(S)-1-[(R)-1-(carbamoylmethyl)-5-oxopyrrolidin-2-yl]car-
bonyl]pyrrolidin-2-yl]ethyl]indole-6-carboxamide,
methyl-2-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-
carbonyl]piperidiny]acetate,
1-ethyl-2-[2-[(S)-1-[(3-piperidiny]carbonyl]pyrrolidin-2-yl]ethyl]indole-6
35 -carboxamide,

ethyl 1-[2-[(S)-2-[2-(6-amidino-1-ethylindol-2-yl)ethyl]pyrrolidinyl]-2-oxoethyl]pyrrolidine-2-carboxylate,
 ethyl 2-[2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]-6-amidinoindolyl]acetate,
 5 2-[2-[(S)-1-[(R)-1-acetylpyrrolidin-2-yl)carbonyl]pyrrolidin-2-yl]ethyl]-1-(carbamoylmethyl)indole-6-carboxamide, and
 6-[2-[(S)-1-(2-phenylacetyl)pyrrolidin-2-yl]ethyl]naphthalene-2-carboxamide.

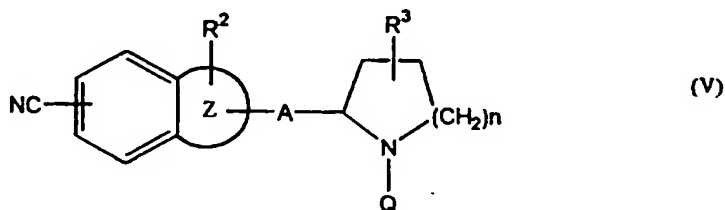
10 4. A thrombin inhibitor composition containing as an active component the compound of formula (I) as defined in claim 1 or the pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

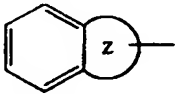
15 5. The thrombin inhibitor composition as defined in claim 4, which is useful for prevention and treatment of thrombosis.

6. The thrombin inhibitor composition as defined in claim 4, which is formulated into the oral preparation.

20 7. A process for preparing the compound of formula (I) as defined in claim 1 and its salts characterized in that:

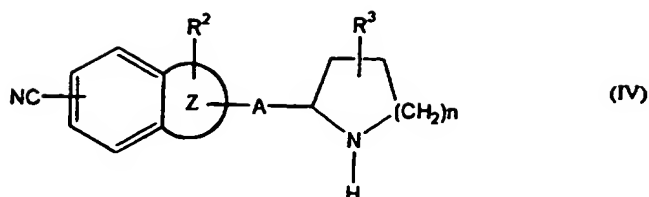
(a) an amino-protecting group of a compound of formula (V):

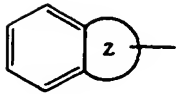


30 wherein , R², R³, A and n are defined as in claim 1 and Q represents an amino-protecting group, is removed to obtain a compound of formula (IV):

35

247

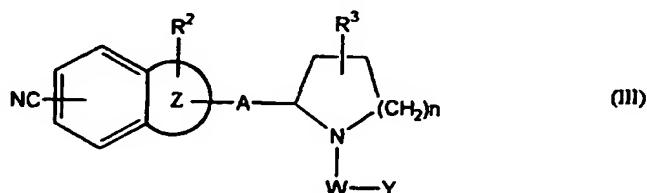


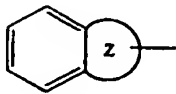
wherein , R^2 , R^3 , A and n are defined as in claim 1;

- 10 (b) the nitrile compound of formula (IV) thereby obtained is reacted with a compound of formula (VI):



15 wherein Y and W are defined as in claim 1 and D represents hydroxy or halogen, to obtain a compound of formula (III):



25 wherein , R^2 , R^3 , A, Y, W and n are defined as in claim 1;

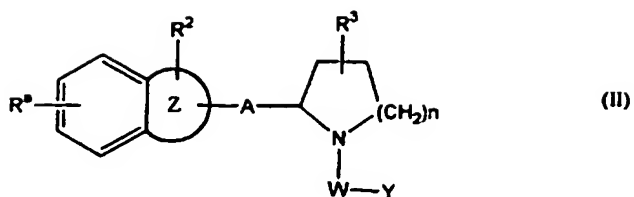
- (c) the compound of formula (III) is reacted with an alcohol compound of formula (VII):



wherein R^1 is defined as in claim 1, in the presence of a hydrogen halide to obtain a compound of formula (II):

35

248



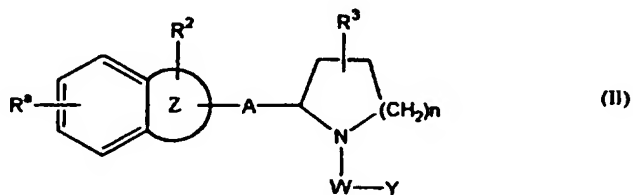
wherein , R^2 , R^3 , A, Y, W and n are defined as in

claim 1 and R^a is a group of formula or

wherein R^1 is defined as in claim 1; and

(d) the compound of formula (II) is reacted with ammonia.

8. A compound of formula (II):



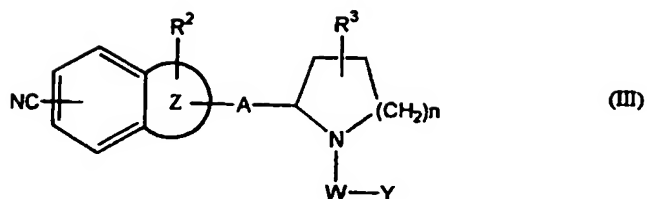
and its salt, wherein , R^2 , R^3 , A, Y, W and n are defined

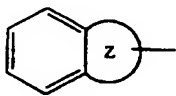
as in claim 1 and R^a is a group of formula or

wherein R^1 is defined in claim 1.

9. A compound of formula (III):

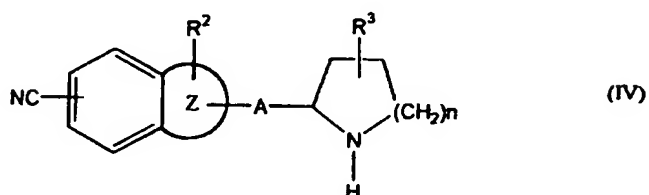
249

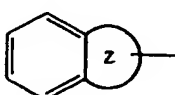


and its salt, wherein , R^2 , R^3 , A, Y, W and n are defined as in claim 1.

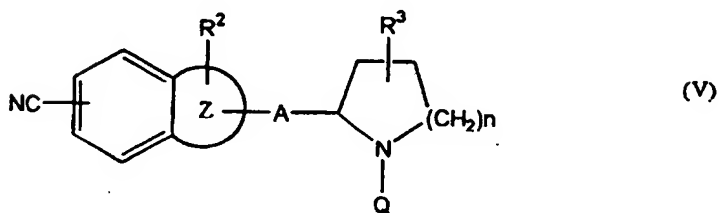
10

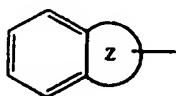
10. A compound of formula (IV):



20 and its salt, wherein , R^2 , R^3 , A and n are defined as in claim 1.

25 11. A compound of formula (V):

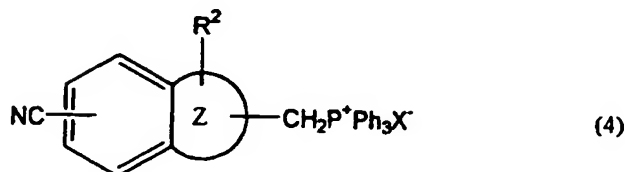


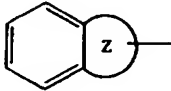
and its salt, wherein , R^2 , R^3 , A and n are defined as in claim 1 and Q represents an amino-protecting group.

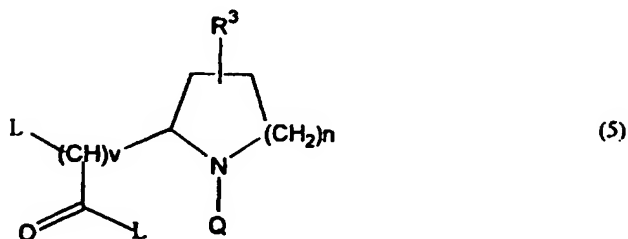
35

250

12. A process for preparing the compound of formula (V) as defined in claim 11 and its salt, which comprises reacting compound of formula (4):

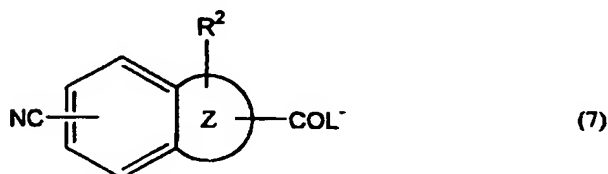


10 wherein  and R² are defined as in claim 1, with a compound of formula (5):

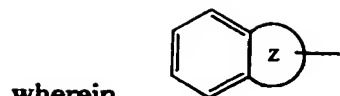


20 wherein R³ and n are defined as in claim 1, two L groups may be same or different and represent hydrogen, alkyl, alkoxycarbonyl or alkoxy-carbonylalkyl, Q represents an amino-protecting group, X represents halogen, and v denotes an integer of 0 to 2.

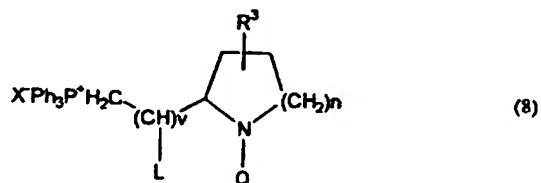
25 13. A process for preparing the compound of formula (V) as defined in claim 11 and its salt, which comprises reacting a compound of formula (7):



35



and R^2 are defined as in claim 1 and L represents hydrogen, alkyl, alkoxycarbonyl or alkoxycarbonylalkyl, with a compound of formula (8):



wherein R^3 and n are defined as in claim 1, Q represents an amino-protecting group, X represents halogen, L represents hydrogen, alkyl, alkoxycarbonyl or alkoxycarbonylalkyl and v denotes an integer of 0 to 2.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 97/00100

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: C 07 D 403/06, 401/06, 405/06, 409/06, 207/08, 207/10; A 61 K 31/40, 31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: C 07 D 403/00, 405/00, 409/00, 207/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chemical Abstracts

Electronic data base consulted during the international search (name of data base used, where practicable, search terms used)

Questel: DARC, CAS; EPO: WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	Chemical Abstracts, Vol.125, No.11, 09 September 1996 (Columbus, Ohio, USA), page 28, column 1, abstract No.131628h, IWANOWICZ, E.J. et al.: "Derivatives of 5-amidine indole as inhibitors of thrombin catalytic activity", & Bioorg. Med. Chem. Lett. 1996, 6(12), 1339-1344 (Eng).	1-13
A	Chemical Abstracts, Vol.99, No.5, 01 August 1983 (Columbus, Ohio, USA), page 501, column 1, abstract No.38220d, KOWA CO., LTD.: "Phenyl esters", & Jpn. Kokai Tokkyo Koho JP 58 13,549 [83 13,549].	1-13
A	Chemical Abstracts, Vol.98, No.9, 28 February 1983 (Columbus, Ohio, USA), page 19, column 2, abstract No.65141q, TIDWELL, R.R. et al.: "Aromatic amidines. Comparison of their ability to block respiratory syncytial virus induced cell fusion and to inhibit plasmin, urokinase, thrombin, and trypsin", & J. Med. Chem. 1983, 26(2), 294-8.	1-13

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 August 1997 (07.08.97)

Date of mailing of the international search report

19 August 1997 (19.08.97)

Name and mailing address of the ISA/ AT
AUSTRIAN PATENT OFFICE
Kohlmarkt 8-10
A-1014 Vienna
Facsimile No. 1/53424/535

Authorized officer

Hammer

Telephone No. 1/53424/374

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 97/00100

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Vol.123, No.23, 04 December 1995 (Columbus, Ohio, USA), page 50, column 1, abstract No.306203d, BAJUSZ, S. et al.: "Active site-directed thrombin inhibitors: α -hydroxyacyl-prolyl-arginals. New orally active stable analogs of δ -Phe-Pro-Arg-H", & Bioorg. Med. Chem. 1995, 3(8), 1079-89 (Eng).	4-6
A	Chemical Abstracts, Vol.124, No.5, 29 January 1996 (Columbus, Ohio, USA), page 3, column 2, abstract No.44457n, KIMBALL, S.D.: "Challenges in the development of orally bioavailable thrombin active site inhibitors", & Blood Coagulation Fibrinolysis 1995, 6(6), 511-19 (Eng).	4-6
A	US 4 258 192 A (OKAMOTO) 24 May 1992 (24.05.92), claim 1; column 4, line 65 - column 6, line 44 (cited in the application). -----	4-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR 97/00100

Le Recherchenbericht angeführtes Patentdokument in search report Document de brevet cité dans le rapport de recherche		Datum der Veröffentlichung Publication date Date de publication		Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets		Datum der Veröffentlichung Publication date Date de publication	
US A	4258192	24-03-81		CA A1	1131621	14-09-82	
				US A	4201863	06-05-80	
				US A	4133880	09-01-79	
				US A	4049645	20-09-77	
				US A	4062963	13-12-77	
				US A	4066758	03-01-78	
				US A	4066759	03-01-78	
				US A	4069318	17-01-78	
				US A	4069329	17-01-78	
				US A	4072743	07-02-78	
				US A	4072744	07-02-78	
				US A	4072757	07-02-78	
				US A	4073891	14-02-78	
				US A	4073892	14-02-78	
				US A	4073916	14-02-78	
				US A	4125619	14-11-78	
				US A	4139529	13-02-79	
				US A	4154828	15-05-79	
				US A	4168307	18-09-79	
				US A	4041156	09-08-77	
				US A	4046876	06-09-77	
				US A	4055636	25-10-77	
				US A	4055651	25-10-77	
				US A	4066773	03-01-78	
				US A	4069317	17-01-78	
				US A	4069323	17-01-78	
				US A	4070457	24-01-78	
				US A	4073913	14-02-78	
				US A	4073914	14-02-78	
				US A	4096255	20-06-78	
				US A	4097472	27-06-78	
				US A	4097591	27-06-78	
				US A	4101653	18-07-78	
				US A	4104392	01-08-78	
				US A	4108986	22-08-78	
				US A	4173630	06-11-79	
				US A	4140681	20-02-79	
				US A	4117127	26-09-78	
				US A	4131673	26-12-78	
				AT A	9051776	15-09-79	
				AT B	356304	25-04-80	
				AU A1	20350776	15-06-78	
				CA A1	1102316	02-06-81	
				CA A2	1137469	14-12-82	
				CA A2	1140917	08-02-83	
				CH A	630348	15-06-82	
				CH A	630349	15-06-82	
				CS B2	2281103	16-04-84	
				CS B2	2281113	16-04-84	
				CS F	2281103	14-05-84	
				CS F	2281113	14-05-84	
				DD C	128681	07-12-77	
				DE A1	2655636	23-06-77	
				DE C2	2655636	11-03-93	
				DK A	5505776	10-06-77	
				DK B	154289	31-10-88	
				DK C	154289	28-03-89	
				FI A	763528	10-06-77	
				FI B	65240	30-12-83	
				FI C	65240	10-04-84	
				FR A1	2334349	08-07-77	
				FR B1	2334349	22-07-83	
				GB A	1538206	17-01-79	
				GB A	1538207	17-01-79	
				GR A	63103	05-09-79	
				HU P	175799	28-10-80	
				IL A0	51005	31-01-77	
				IL A1	51005	30-09-86	
				JP A2	52097934	17-08-77	
				JP B4	60017782	07-05-85	
				LU A	76347	24-06-77	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR 97/00100

NL	B	177747	17-06-85
NO	A	764186	10-06-77
NO	B	145379	30-11-81
NO	C	145379	10-03-82
NZ	A	182812	24-08-84
PL	P	106642	31-01-80
PL	B1	111920	30-09-80
PT	B	65934	13-06-78
SU	A3	965353	07-10-82
US	A	4125604	14-11-78
AT	A	2053779	15-12-81
AT	B	367750	26-07-82
ES	A5	434098	21-02-78
ES	A1	454098	16-03-78
ES	A1	466094	01-10-78
SE	A	7613799	10-06-77
SE	B	438680	29-04-85
SE	C	438680	08-08-85
AT	A	399778	13-05-82
AT	A	3284780	15-05-82
AT	A	3285780	15-05-82
AT	B	369356	27-12-82
AT	B	369357	27-12-82
AT	B	369358	27-12-82
CH	A	633773	31-12-82
CH	B2	648293	15-03-85
CS	B2	236757	15-03-85
CS	B2	236772	15-03-85
CS	B2	236773	15-03-85
DD	C	137352	29-08-79
DE	A1	2801478	20-07-78
DE	C2	2801478	31-01-91
DK	A	263778	20-07-78
DK	B	150521	16-03-87
DK	C	150521	19-10-87
ES	A6	466706	03-10-78
ES	A2	466706	16-10-78
ES	A2	466705	16-08-79
ES	A6	466705	27-08-79
FI	A	780073	20-07-78
FI	A	842539	31-06-84
FI	A0	842539	31-06-84
FI	B	72316	30-01-87
FI	C	72316	11-05-87
FI	B	74455	30-10-87
FI	C	74455	08-02-88
FR	A2	2378004	18-08-78
FR	B2	2378004	13-09-85
GB	A	1596971	03-09-81
HU	B	180265	28-02-83
IL	A0	53685	10-03-78
IL	A1	53685	31-12-85
IT	A	1126229	14-05-86
JP	A2	54100342	08-08-79
JP	B4	62014548	02-04-87
LU	A	78911	28-09-78
NL	C	187746	02-01-92
NO	A	780191	20-07-78
NO	B	158681	11-07-88
NO	C	158681	19-10-88
NZ	A	186198	19-12-80
PH	A	15913	22-04-83
SE	A	7800512	20-07-78
SE	B	452624	07-12-87
SE	C	452624	17-03-88
SU	A3	938739	23-06-82
SU	A3	1181539	23-09-85
AT	E	1450	15-08-82
AU	A1	50486779	06-03-80
AU	B2	520342	28-01-82
CA	A1	1135698	16-11-82
CS	P	228119	14-05-84
DD	C	146600	18-02-81
DE	C0	2963539	07-10-82
DK	A	3645779	01-03-80
DK	B	152495	07-03-88
DK	C	152495	25-07-88
EP	A1	8746	19-03-80
EP	B1	8746	11-08-82
ES	A1	483767	16-04-80
ES	A5	483767	24-04-80
FI	A	792637	01-03-80
FI	B	66183	31-05-84
FI	C	66183	10-09-84
GR	A	64905	07-06-80

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR 97/00100

HU	B	179734	28-12-82
IE	B	48623	20-03-85
IL	A0	58131	30-12-79
JP	A2	55033499	08-03-80
JP	B4	1035000	21-07-89
NO	A	792823	03-03-80
NO	B	151888	21-01-80
NO	C	151888	08-03-85
NZ	A	191434	06-07-84
PH	A	15662	11-03-83
PL	A1	218008	05-05-80
PL	B1	121663	31-05-82
PT	A	70130	01-08-79
SU	A3	1042615	15-09-83
ZA	A	7904581	29-04-81
PL	D	204063	30-07-79
PL	B1	123267	30-10-82
ZA	A	7800123	29-08-79
AU	A1	32289778	19-07-79
AU	B2	522320	27-05-82
US	A	4093712	06-06-78
NL	A	7800448	21-07-78
BE	A4	863092	19-07-78
NL	B	187746	01-08-91
CA	A1	1073914	18-03-80
DE	A1	2550088	20-05-76
DK	A	4989775	09-05-76
FR	A1	2290193	04-06-76
FR	B1	2290193	18-08-78
GB	A	1516668	05-07-78
JP	A2	51125264	01-11-76
JP	B4	59039424	22-09-84
NO	A	753733	11-05-76
SE	B	431204	23-01-84
SE	C	431204	03-05-84
JP	A2	51125051	01-11-76
JP	B4	55037992	01-10-80
NL	A	7512637	11-05-76
SE	A	7512530	10-05-76
JP	A2	51125261	01-11-76
JP	B4	59012662	24-03-84
JP	A2	51125052	01-11-76